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Exploring Metal-base Catalysis in Indole C2 Selective Mannich and Alkylnitrile Conjugate Addition Reactions

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Declaration

I, Jonathan Richards, hereby declare that, except where reference has been to other sources that the work contained within this thesis is my original work as part of my PhD degree program. This program of study was commenced August 2014. The thesis has been composed by myself and has not been submitted, in whole or in part, towards any other degree, diploma or qualification.

Signed:

Date:

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Abbrieviations

Å	Angstrom
Ac	Acetyl
Acac	Acetylacetone
Alk	Alkyl
Ar	Aryl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-Binaphthyl
Bn	Benzyl
Boc	*Tert*butoxycarbonate
BOX	Bis(oxazoline)
CDP	Carbodiphosphorane
Cod	Cyclooctadiene
Cp*	Pentamethylcyclopentadiene
^{o}C	Degrees celcius
DBE	Dibenzyl ether
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
Dipp	Diisopropylphenyl
DMA	Dimethylacetamide
DMAP	*N*,*N*-dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
Dppe	Diphenylphosphinoethane
Dppm	Diphenylphosphinomethane
dr	Diastereomeric ratio
DTBP	Ditertbutylperoxide
ee	Enantiomeric excess
Equiv	Equivilents
Et	Ethyl
FLP	Frustrated Lewis pair
h	Hours
HMDS	Hexamethyldisilazide
HMPA	Hexamethylphosphoramide
KIE	Kinetic isotope effect
LED	Light emitting diode
LDA	Lithium diisopropylamide
LTMP	Lithium tetramethylpiperidide
Me	Methyl
MS	Mass spectroscopy
NR	No reaction
NHC	*N*-heterocyclic carbene
NMP	*N*-methylpyrrolidine
NMR	Nucular magnetic resonance
OMP	*Ortho*methoxyphenyl
Ph	Phenyl
PMP	Paramethoxyphenyl
Py	Pyridyl
Pr	Propyl
Quant.	Quantitative
Rt	Room temperature
segphos	4,4′-Bi-1,3-benzodioxole-5,5′diylbis(diphenylphosphane)
TBME	*Tert*butylmethylether

TCE	Tetrachloroethane
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
Tf	Triflate
THF	Tetrahydrofuran
TMS	Tetramethylsilyl
Tol	Toluene
Ts	Tosyl

Lay summary

The molecules used in the pharmaceutical industry often display complex architectures. These species may be built up from smaller subunits. Bringing these pieces together to more complex structures costs energy; commonly more than is present under ambient conditions. While increasing temperature allows the barrier to reactivity for some units to be overcome, this principle is often not the case. For this reason, activated and specialty reagents, known as so-called catalysts, have been used. Catalysts lower the activation barrier required for chemical transformations to take place, but –unlike reagents– are not consumed in the reaction; thus, these species may be recovered after the reaction and re-used. In this thesis the focus has been on catalysing reactions in a way that all molecules of the starting materials end up in the products; no waste is formed. Such a so-called atom-economic transformation has been achieved through the subtle and careful design and tuning of both reagents and products. Indole is a very useful nitrogen-containing unsaturated molecule found in many natural products and drug compounds. Typically, this compound is biased in its intrinsic reactivity, and favours reaction at a specific site of the molecule (at carbon number 3). In this thesis, a metal-based catalyst has been developed that forces an unusual reaction at a different more challenging position (at carbon number 2). This transformation allows the formation of previously unreported and inaccessible products. Another part of work has been devoted to stabilising specific chemical compounds that are highly reactive and may decompose upon exposure to ambient conditions. While this high level of reactivity makes the compounds delicate to handle, the high reactivity may be also channelled to a unique reactivity with other molecules. We have used a metal-free carbon species in its so-called low-oxidation state “0” –as catalysts– in order to facilitate the addition of unreactive compounds, such as commonly used solvents, to so-called unsaturated acceptors; with the aim to create more complex motifs. Metal-based species had been shown to fail to catalyse this transformation. The unique reactivity of these carbon(0) compounds was found to surpass all other potential catalysts examined. This work also represents the first time that such a carbon(0) species has been used as a catalyst at all. The catalytic transformations in both parts of this thesis project have proved to be quite versatile allowing great selectivity for functional groups so to create in a single step rather complex architectures.

Abstract

The focus of this PhD project dealt with the development of base-catalysed transformations towards novel and pharmaceutically relevant molecules.

The first chapter was intended to be an application of our previously reported catalyst, Na–N($SiMe_3$)$_2$, to a new substrate class, i.e., *N*-unprotected indoles. Rather than the anticipated C3-selective Mannich-type addition to imines, which would represent the indole's intrinsic Friedel–Crafts-type reactivity, a reaction mixture containing an unexpected C2-functionalised indole was obtained. The optimisation of this serendipitous transformation led to a three-component catalyst system for this unusual C2–H bond activation: copper(I) chloride, sodium tetrafluoroborate, and lithium carbonate. Key features of this transformation are as follows: rare example of a C2–C(sp^3) bond formation with *N*-unprotected indoles; unprecedented C2-selective Mannich-type reaction with *N*-unprotected indoles; sparse example of the catalytic use of a metal carbonate in organic synthesis. A wide range of both indoles and imines proved to be tolerated under the mild reaction conditions; this transformation was even amenable to a three-component reaction, i.e., the *in situ*-generation of the imines from aldehydes and *ortho*-anisidine. Mechanistic and control experiments were carried out in order to elucidate the identity of the catalytically active species and to gain insight into the C2–H bond activation mode. At this stage, it was suggested that a copper(I)/lithium heterobimetallic carbonate was critical for the C2-selectivity, and a traceless directing-group hypothesis was proposed.

The second chapter of this thesis was focused on the development of the catalytic use of a so-called carbodiphosphorane (CDP), an unusual carbon(0) species, in C–C bond formation. The intended reaction comprised the conjugate addition of aliphatic nitriles to α,β-unsaturated amides; a decent substrate scope was developed. Other organocatalysts including Schwesinger and Verkade super bases as well as carbenes [carbon(II) species] proved to be substantially less efficient; likewise, various metal–bases were found to be poor in reactivity. Key features of this transformation are as follows: unprecedented catalytic use of a CDP in organic synthesis under metal-free conditions; unprecedented example of a carbone catalysis in C–C bond formation; extremely low catalyst loading in the context of organocatalysis (down to 0.25 mol%). Preliminary mechanistic experiments were carried out to identify a plausible pathway, i.e., Lewis base catalysis vs. Brønsted base catalysis.

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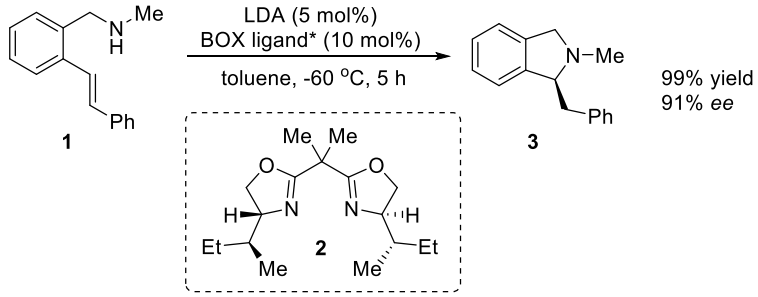
1 Catalytic Indole functionalisation

1.1 Use of metal amides in catalysis

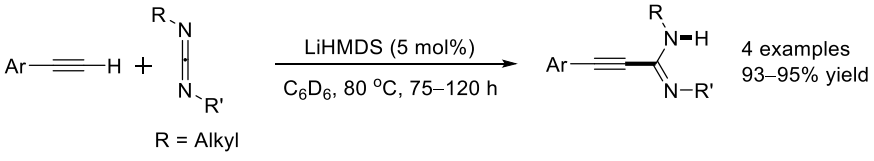
Classical transition metal-catalysed cross-coupling strategies enable the formation of a range of C(sp^2)–C(sp^2),[1] C(sp^2)–C(sp^3),[2] and N–C(sp^3)[3] bonds between various reaction partners. Such efficient transformations have been used extensively in industrial applications for the production of a variety of fine chemicals. However, there are several drawbacks to these processes, chiefly the lack of (complete) atom economy; even for coupling reactions relying on C–H (rather than C–X) bond activation there may be still incomplete incorporation of all starting material components into the product, although the waste production may be minimal (H_2), e.g. in cross dehydrogenative coupling (CDC) reactions.[4,5] In the context of Brønsted base catalysis non-toxic metal species may be used in a deprotonative strategy with 100% atom economy while still producing synthetically useful molecules; such approach would rely on a (formal) C–H or N–H bond activation with subsequent addition across an unsaturation. In particular regarding (toxic) transition metal catalysis, some palladium complexes have been shown to leach metal traces into the reaction mixture that may be intractable from the final product and therefore retained in the final (fine) chemical.[6,7] Regarding Brønsted base catalysis, non-toxic metal compounds were shown to be applicable in (formal) C–H and N–H bond activation strategies. A large focus in this area has been related to catalytic hydroamination reactions.[8] A nice example of such transformations is the catalytic asymmetric formation of isoindolines through intramolecular 5-*exo*-trig C–N bond formation in *ortho*-aminomethyl styrenes (Scheme 1); this type of reaction was catalysed by a chirally modified lithium amide leading to an excellent asymmetric induction in the final product.[9]

Scheme 1: Asymmetric intramolecular hydroamination triggered by a chirally modified lithium amide.



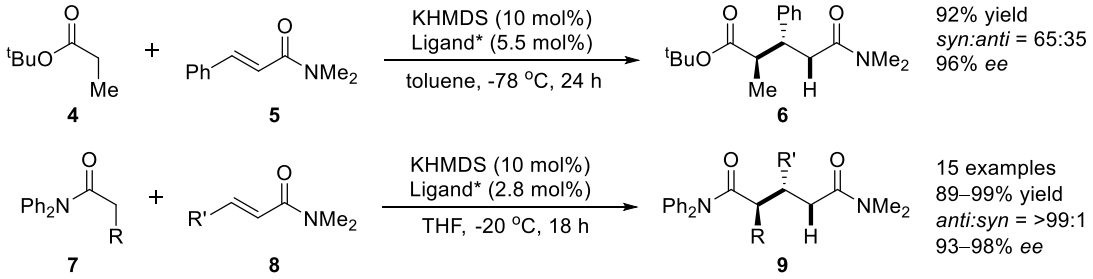
In a similar context, a lithium amide catalyst was used in the intermolecular C–C bond formation between aromatic terminal alkynes and a variety of carbodiimides (Scheme 2).[10] With pK_a values of ~ 29 (in DMSO),[11] phenyl acetylene is a similarly challenging substrate as amines with pK_a values of ~ 26–32 (in DMSO).[12] In the present example, using Li–HMDS (pK_{BH^+} ~ 30; in DMSO), the deprotonative C(sp)–H bond activation proceeded smoothly to generate the corresponding addition products in high yields.

Scheme 2: Lithium amide-catalysed intermolecular C–C bond formations.[10]



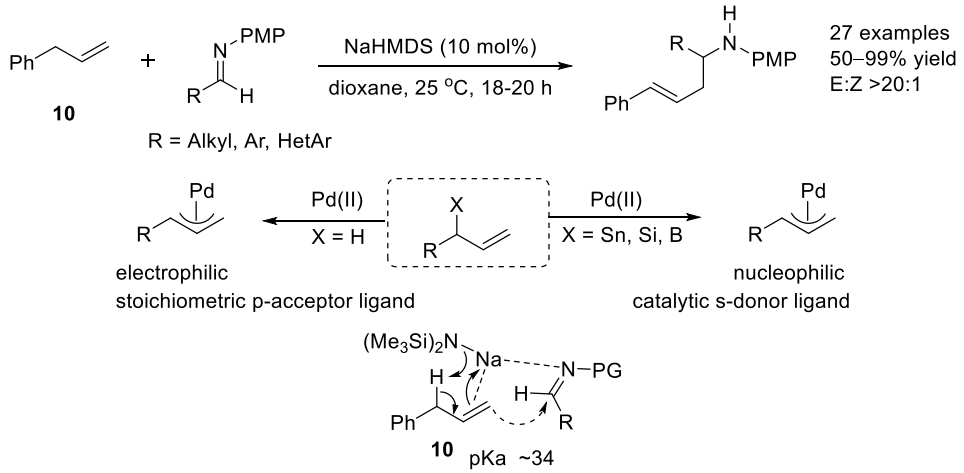
In 2015, Kobayashi *et al.* reported the catalytic asymmetric conjugate addition of esters and amides to various α,β-unsaturated amides (Scheme 3).[13] These reactions were catalysed by a chirally modified potassium amide, and proceeded with modest and excellent *syn*:*anti* ratios for the use of esters and amides, respectively. In addition, alkyl aza-arenes[14] and alkyl sulfonamides[15] have been used as pro-nucleophiles in a similar context. More recently, esters and amides were also shown to add across styrenes under similar potassium amide catalysis conditions.[16] Likewise, O'Shea's base was used to catalytically activate alkyl arenes with subsequent addition to imines[17] and styrenes,[18] which proceeded with the expected regioselectivity.[19]

Scheme 3: Potassium amide-catalysed asymmetric Michael additions of esters and amides.[13]



Earlier work in the Schneider group has addressed the allylic C(sp^3)–H bond activation of aromatic alkenes and their subsequent nucleophilic addition to various aldimines by using Na–HMDS as a sole metal–base catalyst and/or initiator (Scheme 4).[20] The corresponding homoallylic amine products were formed in high yields with complete regioselectivity and with >20:1 *E* selectivity. This transformation was shown to proceed through the *in situ* generation of a nucleophilic allyl–Na intermediate, which represents a significant advance compared to earlier studies. Indeed, when Pd(II) catalysts were used for such C–H bond activation, the resulting allyl–Pd intermediates were revealed to be exclusively electrophilic;[21] nucleophilic allyl–Pd species had been only accessible when allyl–metalloid substrates (Sn, Si, B) were used.[22,23]

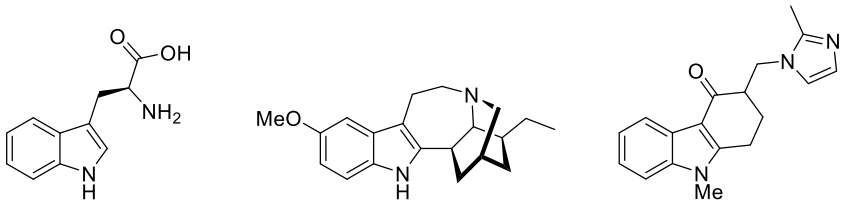
Scheme 4: Sodium amide-triggered allylic C(sp^3)–H bond activation of alkenes.



The broad range of functional group tolerance displayed in both allyl benzenes and aldimines triggered our interest in exploring a similar catalyst system that would lead to a robust and operationally simple functionalisation of important *N*-heterocycles. Due to their presence in the natural amino acid

tryptophan, variously functionalised *N*-unprotected indole motifs appear in many natural products and molecules of pharmaceutical significance; thus, the functionalisation of *N*-unprotected indoles is synthetically significant (Scheme 5).

Scheme 5: Natural products containing 3-substituted indoles.



Tryptophan (**11**)
Natural amino acid

Ibogaine (**12**)
Addiction therapy

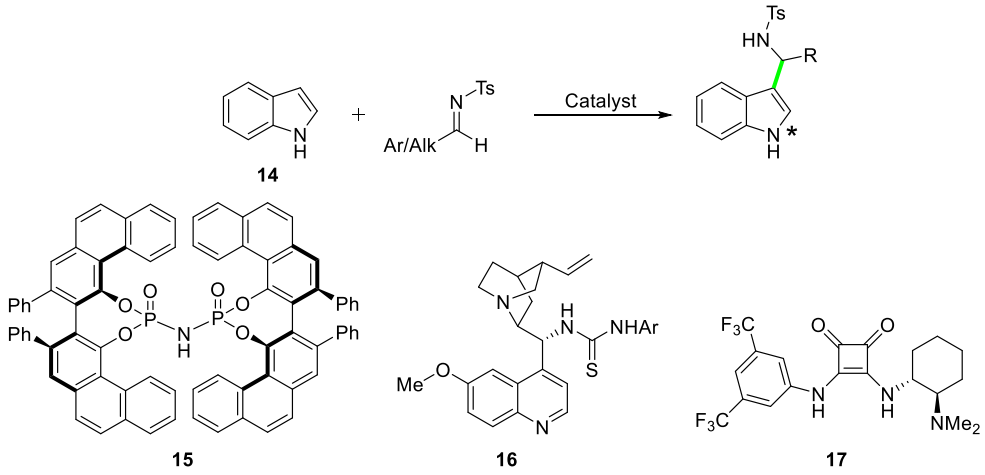
Ondansetron (**13**)
Gastroenteritis

The intrinsic nucleophilic character of this electron-rich heteroaromatic substrate at the C3 position has been exploited in classical Friedel–Crafts-type chemistry. Based on the earlier work in our group, we were interested in using imines as potential electrophiles, i.e. developing catalytic Mannich-type C–C bond formations. Several examples of such chemistry were reported in the literature prior to our investigations. Indeed, a variety of enantiomerically enriched hydrogen bond donors were used to mediate catalytic asymmetric C3-selective Mannich-type reactions between *N*-unprotected indoles and imines.

1.2 Catalytic transformations of *N*-unprotected indoles

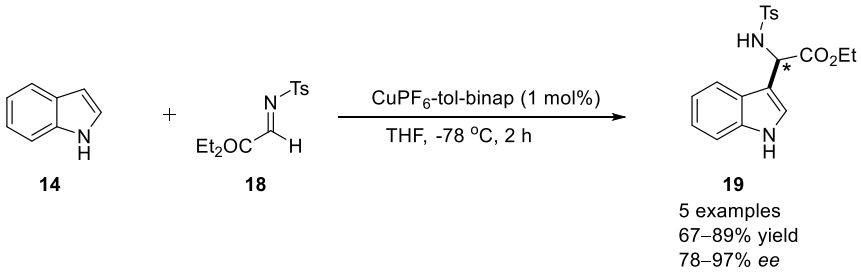
The combined use of *N*,*N*-dimethylaminopyridine (DMAP) and enantiomerically enriched bis(phosphonyl)imides proved to be effective for the use of both aromatic and aliphatic *N*-tosyl-protected aldimines (Scheme 6).[24,25] An enantiomerically enriched cinchona alkaloid-derived thiourea[26] and an enantioenriched squareamide[27] was used as a catalyst for the same transformation (Scheme 5).

Scheme 6: Organocatalytic asymmetric C3-selective Mannich reaction with an *N*-unprotected indole.



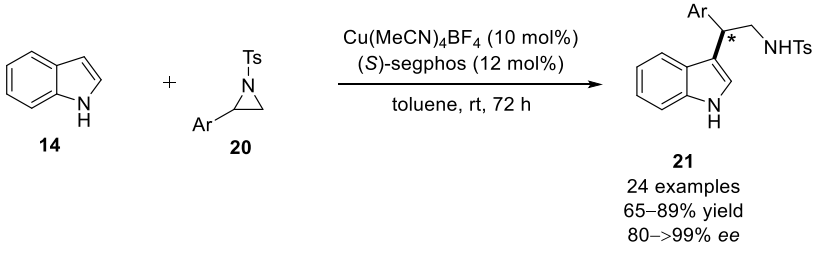
In addition to organocatalysis, chiral metal phosphine complexes have been used for the Mannich reaction between indoles and a glyoxal derived tosyl-imine (Scheme 7).[28] This transformation has been catalysed by several different systems.[29-32]

Scheme 7: Metal catalysed asymmetric C3-selective Mannich reaction with an *N*-unprotected indole.



Aziridines[33] as well as epoxides[34] and nitroalkenes[35] have also been successfully used as electrophiles. Good yields and high *ee*s were achieved.

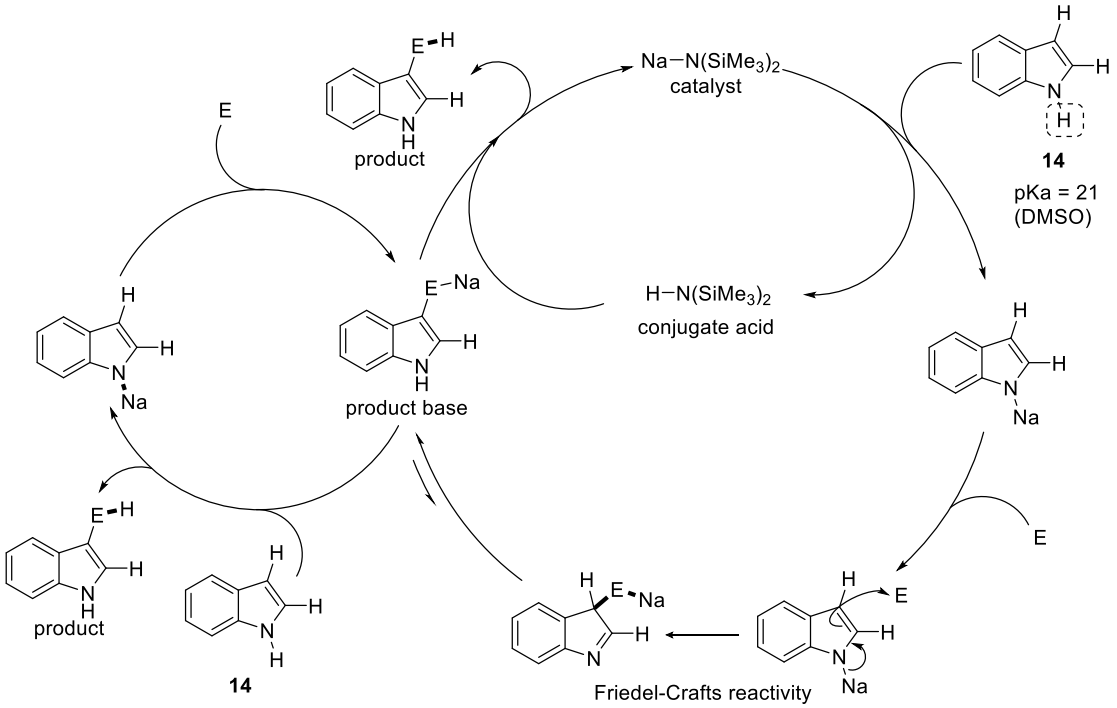
Scheme 8: Formation of tryptophan derivatives via ring asymmetric ring opening of aziridines.



1.3 Aims

We aimed to build on the knowledge and experience gained in the previous work with regards to the concept of metal–amide catalysis. The aim was to explore unbiased *N*-heterocycles, such as *N*-unprotected indoles and derivatives, as synthetically challenging pro-nucleophiles in catalytic C–C bond formations. More specifically, we wanted to exploit the indole's intrinsic Friedel–Crafts reactivity (C3 regioselectivity) with a variety of electrophiles: preferentially imines (Mannich-type chemistry); alternatively Michael acceptors and strained ring systems. While the corresponding reaction products may be literature-known through other catalytic processes (*vide supra*), the approach would be conceptually different. Our metal-base approach would rely on the deprotonation of the indole's "enamine" moiety thus forming an "enamide" that could add more smoothly to a suitable electrophile (Figure 1). A Lewis acid activation of the electrophile by the present metal ion (of the catalyst) would further facilitate the intended C–C bond formation to form initially a Wheland intermediate, which would tautomerize to the functionalised product-base. In order to provide turn-over, the product-base may be protonated either by the conjugate acid of the catalyst (catalysis; right cycle), or by another molecule of the indole starting material (initiation; left cycle).

Figure 1: Concept of metal–amide-triggered Friedel–Crafts chemistry with *N*-unprotected indoles.



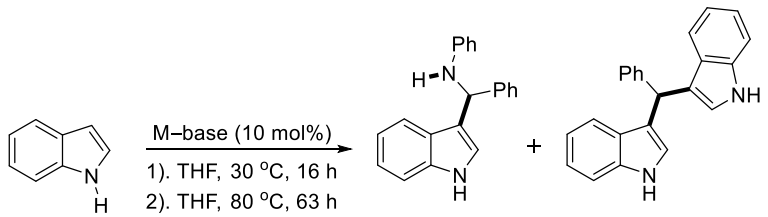
Through the use of a chiral amide[36] it was believed enantioselectivity can be achieved.

1.4 Reaction optimisation

1.4.1 Initial investigation into the metal–base–catalysed Mannich reaction.

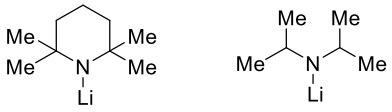
In light of the significant impact of both metal Lewis acid and Brønsted base moiety on the activity of the corresponding metal–base catalyst in the allylic C(sp^3)–H bond activation,[20] a screening of various metal–bases was carried out using *N*-unprotected indole and the benzaldehyde-derived *N*-phenyl-protected imine in THF at 30 °C (Scheme 9). In the earlier work dioxane was used leading to the recovery of starting materials in most cases (except Na–HMDS and K–HMDS), whereas the use of THF resulted in a generally higher activity of metal amides (albeit with low product selectivity). In the present case, the reactions were heated to 80 °C when only starting materials were observed in the initial run. Based on the pK_a value of ~21 for the indole's N–H moiety (in DMSO)],[37] it was expected that the strong metal–base catalysts used would form the metallated enamide required for subsequent nucleophilic addition to the imine. However, similar to the study with allyl benzene as pro-nucleophile, the catalytic use of alkali metal hydrides as well as s-, p-, d-, and f-block metal amides proved to be inefficient. Under forcing conditions, the use of K–HMDS as catalyst afforded the product of double addition [bis(C3)] **23** in 4% yield; the expected C3 product (**24**) was not detected.

Scheme 9: Initial metal–base screening.[a]



Li—H Na—H K—H

no reaction[b]



no reaction[b]

Li—N(SiMe$_3$)$_2$ Na—N(SiMe$_3$)$_2$ K—N(SiMe$_3$)$_2$

no reaction 4% C3' (80 °C)

Zn—[N(SiMe$_3$)$_2$]$_2$ Sn—[N(SiMe$_3$)$_2$]$_2$

no reaction[b]

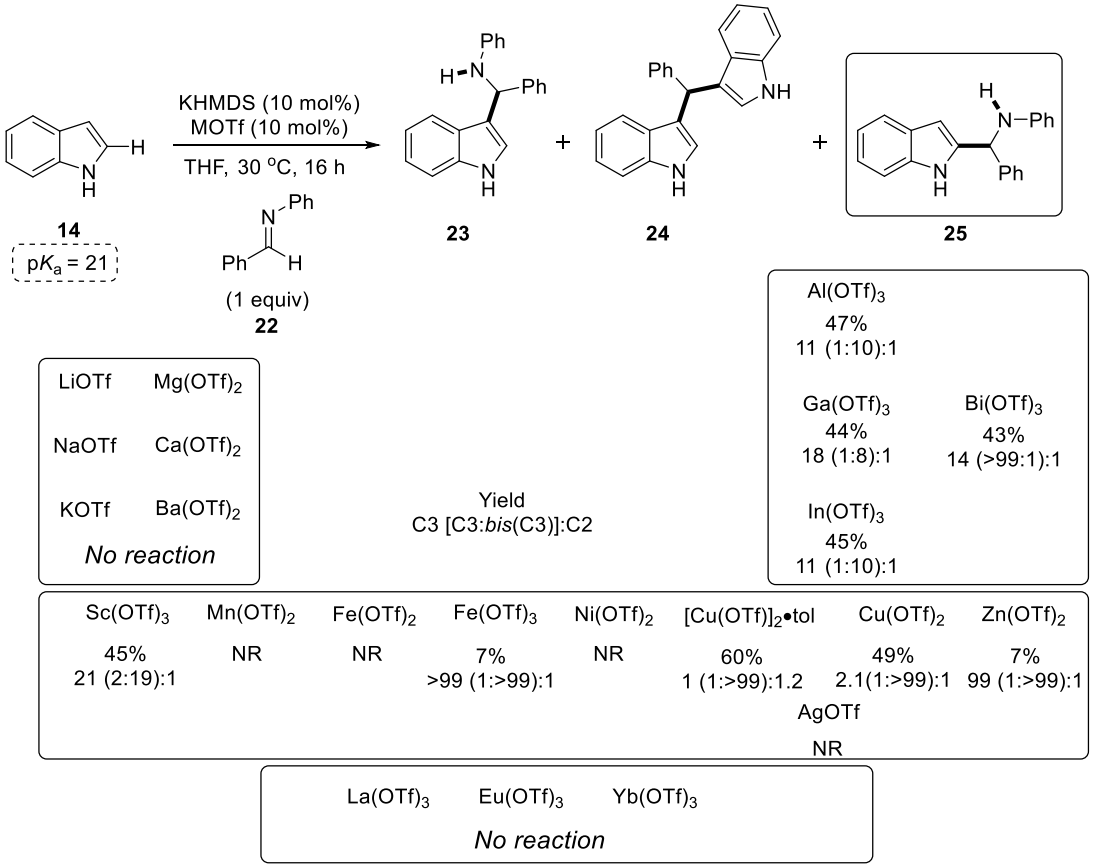
La—[N(SiMe$_3$)$_2$]$_3$ Ce—[N(SiMe$_3$)$_2$]$_3$ Eu—[N(SiMe$_3$)$_2$]$_3$ Gd—[N(SiMe$_3$)$_2$]$_3$ Yb—[N(SiMe$_3$)$_2$]$_3$

no reaction[b]

[a] The NMR yield was determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (DBE) as the internal standard. [b] 50 mol% catalyst loading.

It was postulated that enhancing the electrophilicity of the imine through coordination to an external metal Lewis acid may switch on reactivity for this model transformation. Thus, under otherwise identical reaction conditions, K–HMDS (10 mol%) was used as a Brønsted base catalyst in combination with various commercially available metal triflates as Lewis acid co-catalyst (10 mol%; Scheme 10). The use of alkali metal, alkaline earth metal, and rare earth metal triflates resulted only in the recovery of starting materials. However, when certain main group and transition metal triflates were used, three products could be identified: the expected mono-adduct in C3 position **23**,[37] the corresponding double addition product **24**, and the unexpected mono-adduct in C2 position **25**. The use of main group metal triflates favored the Friedel–Crafts products **23** and **24**. Generally, among the reactive transition metal triflates, the formation of the double-adduct **24** was predominant. Interestingly however, the use of copper triflates displayed a higher level of the unusual C2 selectivity.

Scheme 10: Influence of external metal Lewis acid catalyst on both reactivity and selectivity.



[a] Both conversion and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture. [b] NR = no reaction; no products were detected – only starting materials were recovered.

The unexpected C2 regioselectivity is of significance and substantial value for several reasons:

(1) The pK_a value of the C2–H bond is substantially higher than the one of the N–H bond (38.1 vs. 21);[38] thus, the C2-selective transformation is much more challenging than the common Friedel–Crafts textbook chemistry.

(2) A variety of natural products and drugs contain an *N*-unprotected indole core, functionalized in C2 position (Figure 3).

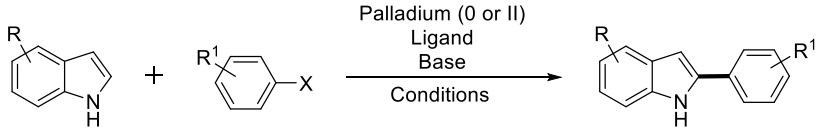
(3) There is an interesting reminiscence with the initially C2-selective oxidation chemistry of tryptophane and its derivatives in Nature (Scheme 13).

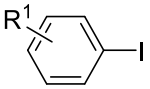
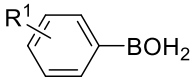
(4) There is limited precedence in synthetic organic chemistry regarding the selective formation of $C(sp^2)$–$C(sp^3)$ bonds in the present context. The most important examples are outlined below.

1.4.2 Contextualization of the Unexpected C2 Functionalisation of *N*-Unprotected Indoles

Literature precedence of indole C2 functionalisations has been dominated by rather common arylation chemistry, i.e. C(sp^2)–C(sp^2) bond formation through e.g. palladium-catalysed cross coupling reactions (Table 1). While several different approaches with regards to coupling partner, catalyst and conditions, appear in the literature the overall scope and reactivity is generally poor. Incorporation of a protecting groups which functions to direct metalation to C2 have been exploited to allow C-2: amination[39-43], cyanation[44-46], alkenylation[47-54], and phosphoramidation[55].

Table 1: C2-selective arylation of indoles using neutral coupling partners.



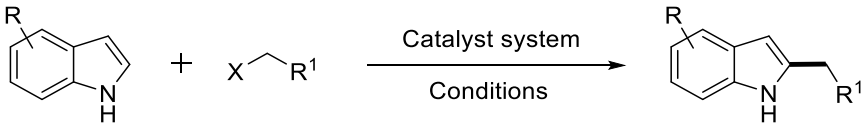
Entry	Coupling partner	Catalysts/Activators	Conditions	Scope and yield
1		$Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%), MgO (1.2 equiv.)	Dioxane/DMF (1:2), 150 °C, 18 h	7 examples 39–87%[56]
2		$Pd(OAc)_2$ (5 mol%), CuI (2 equiv.)	DMF, 140 °C, 48 h	1 example 35%[57]
3	 **26**	$Pd(OAc)_2$ (1 mol%), CsOAc (2.8 equiv.)	DMA, 125 °C, 24–48 h	7 examples 23–66%[58]
4		$Pd(OAc)_2$ (5 mol%), AcOK (3 equiv.), dppm (5 mol%)	H_2O, 110 °C, 24 h	11 examples 42–79%[59]
5		$PdCl_2(MeCN)_2$ (10 mol%), K_2CO_3 (2 equiv.), norbornene (2 equiv.)	DMA, H_2O 70 °C, 17 h	20 examples 26–99%[60]
6	 **27**	$Pd(OAc)_2$ (5–10 mol%),	AcOH, O_2 (1 atm), RT, 10 h	15 examples 50–83%[61]
7		Pd^0/MIL-101 (0.5 mol%)	DCM/ AcOH (1:4), O_2, 60 °C, 4 h	5 examples 58–84%[62]

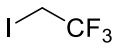
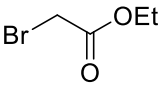
These reactions typically form C(sp^2)–C(sp^2)-coupled products in contrast to our observed C(sp^2)–C(sp^3) products. With respect to the latter transformation, far fewer reactions have been described.[63,64]

Unbiased alkylation has also been reported more recently again typified by palladium chemistry. The use of norbornene as a traceless directing group analogous to the Catellani reaction[65] has gathered considerable following and been used successfully for several indole C(sp^2)–(sp^3) couplings[66]. This

ortho C–H functionalisation proceeds in a similar fashion to that reported in Figure 2 using aryl halides. Alkyl iodides[67], α-bromo esters[68], and alkyl bromides have all been successfully coupled[69].

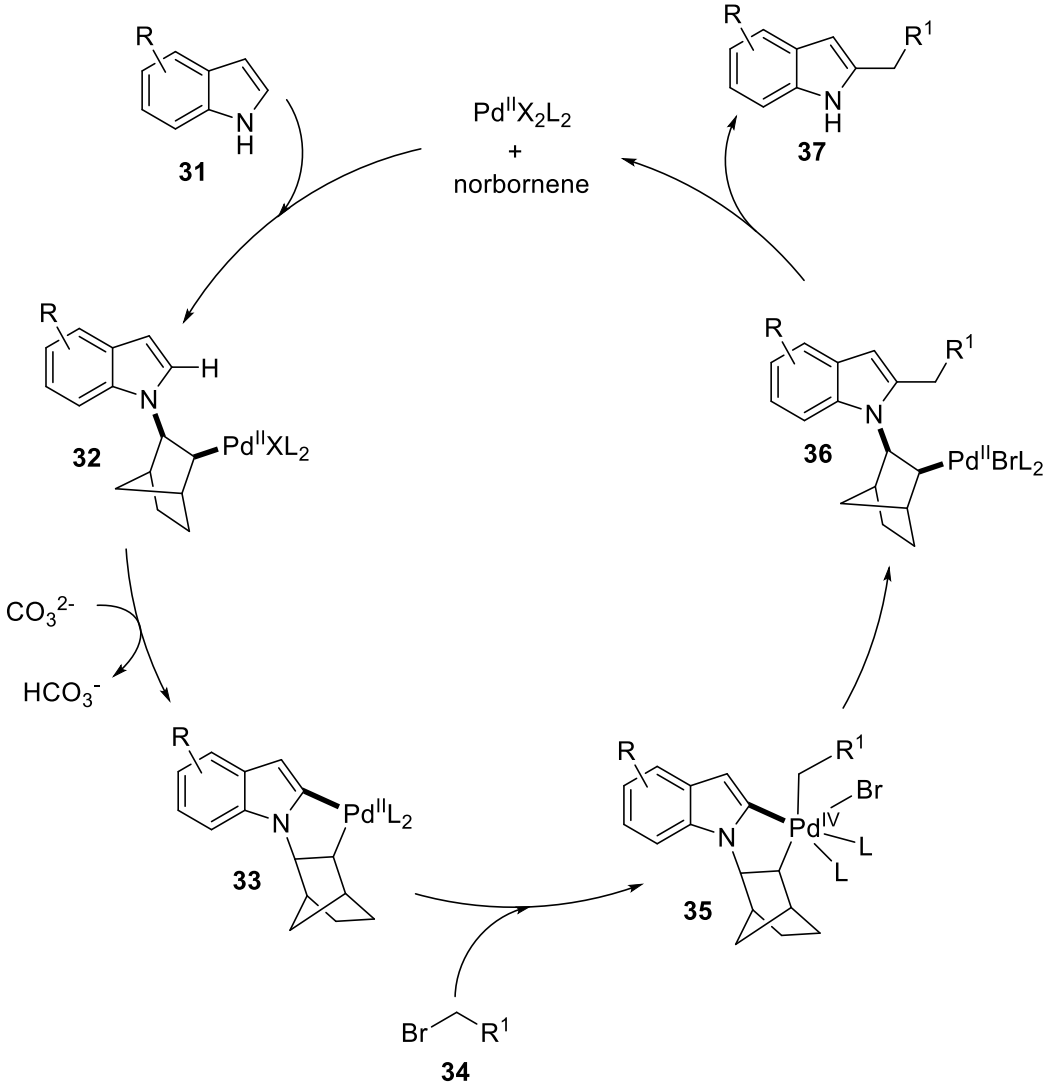
Table 2: Catalytic C2-alkylation of *N*-unprotected indoles.



Entry	Coupling partner	Catalysts/Activators	Conditions	Scope and yield
1	 **28**	$Pd(acac)_2$ (15 mol%), dibenzoylmethane (0.4 equiv), norbornene (2 equiv.), $KHCO_3$ (2 equiv.)	DMF, 100 °C, 24 h	12 examples 13–82%[70]
2	 **29**	$Pd(PhCN)_2Cl_2$ (10 mol%), norbornene (2 equiv), $NaHCO_3$ (4 equiv)	DMF/H_2O (2:1), 70 °C, 14 h	14 examples 65–91%[71]
3	 **30**	$PdCl_2(MeCN)_2$ (10 mol%) Norbornene (2 equiv) K_2CO_3 (2 equiv)	DMA 70–90 °C, 14–61 h	21 examples 43–82%[72]

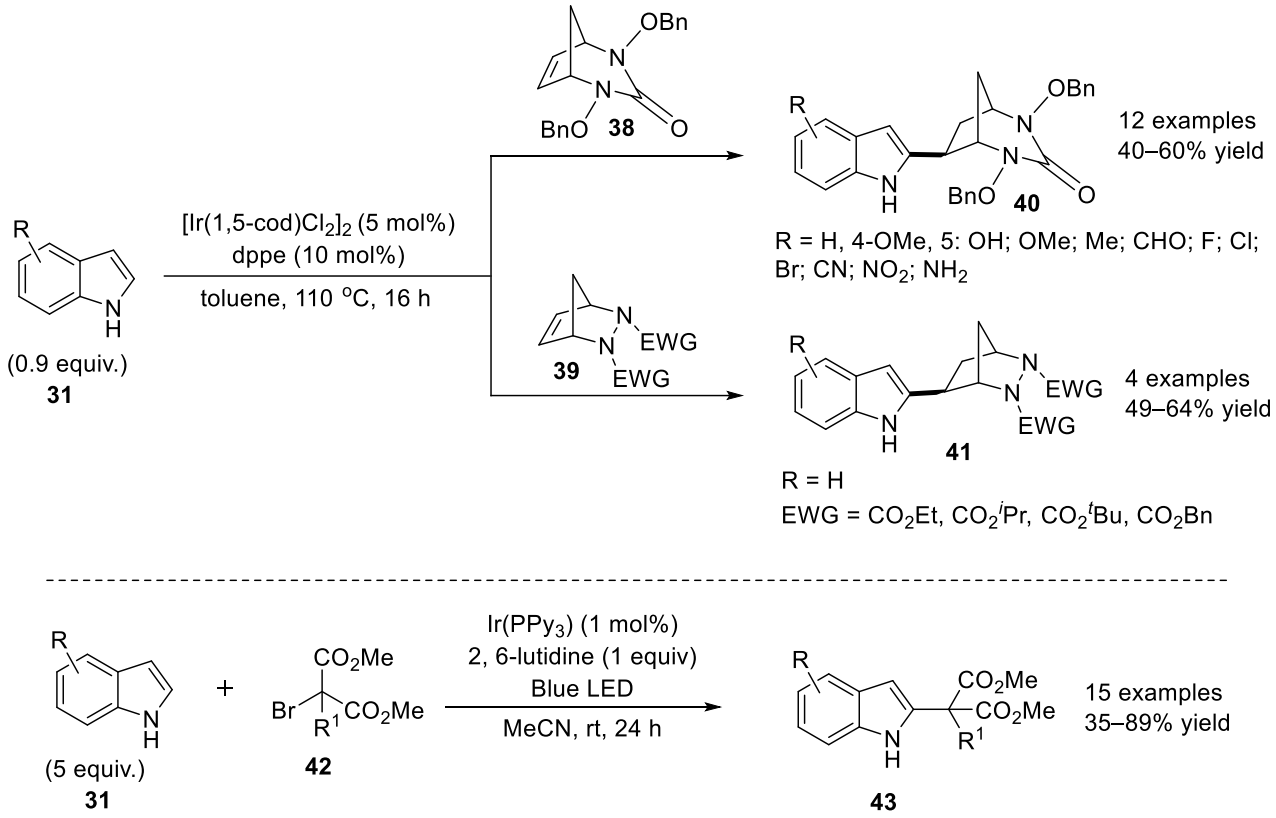
The initial assumption was that the indole added to the norbornene through the enamine at C3. This sets up carbopalladation to C2 allowing further functionalisation. Through mechanistic investigation the true pathway was shown to go via a *N*-palladation rather than C3. Deprotonation of NH and addition to norbornene forms **32**. Carbometallation and deprotonation at C2 forms palladacycle **33**. After oxidative addition of alkyl halide and reductive elimination **36** is formed before elimination of the norbornene protecting group.[71]

Figure 2: Ir-catalysed C2-alkylation of *N*-unprotected indoles using a traceless directing group.



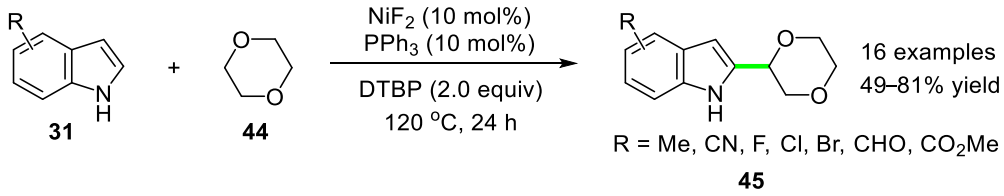
In addition to the norbornene directed alkylation, iridium has been used for the incorporation of unusual alkyl fragments. Bicyclic olefins were efficiently introduced at the C2 position with good substrate scope for the indole fragment.[72] In addition photocatalytic C2–H functionalisation with alkyl bromides was achieved with $Ir(PPy_3)$ and blue LEDs (Scheme 11).[69]

Scheme 11: Ir-catalysed C2-alkylation of *N*-unprotected indoles.



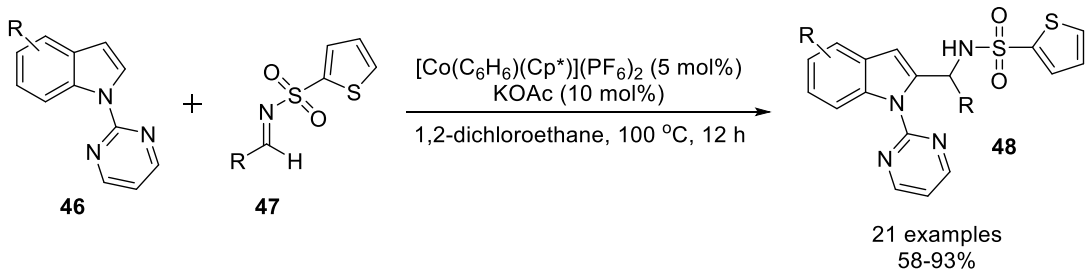
Cai *et al.* reported recently on a Ni-catalysed C2-selective dehydrogenative cross-coupling of *N*-unprotected indoles with cyclic ethers (Scheme 12). This reaction demonstrates good functional group tolerance for both indoles and cyclic ethers.

Scheme 12: Ni-catalysed C2-selective dehydrogenative cross-coupling of indoles with cyclic ethers.



To the best of our knowledge, the only example of a C2-selective Mannich-type reactivity of the indole core was reported by Kanai *et al.* (Scheme 13)[73]. However, their cobalt catalysis relies on the use of *N*-pyrimidyl-protected indoles **46** to induce metalation at C2 with subsequent C–C bond formation using highly electrophilic *N*-sulfonyl-protected imines **47**. Here, it is noted that a reaction was not observed when *N*-unprotected indoles and/or less electrophilic *N*-Boc-protected imines were used.

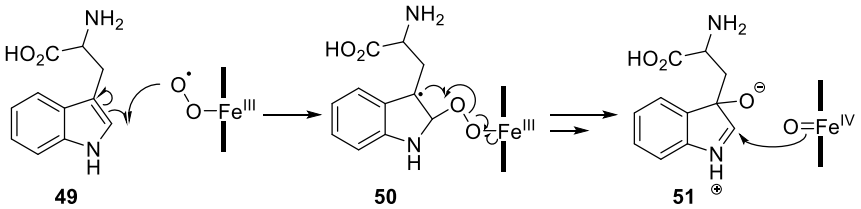
Scheme 13: Co-catalysed C2-selective Mannich-type reactions with *N*-pyrimidyl-protected indoles



1.4.3 Significance in pharmaceuticals and natural products

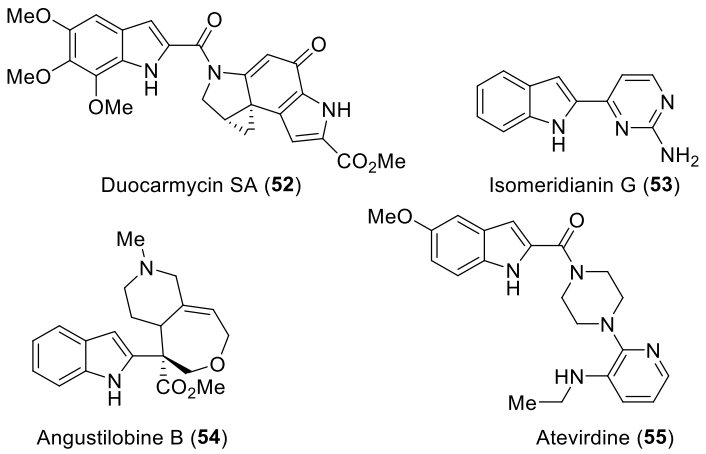
The indole core derived from the natural aminoacid tryptophan is a common motif in naturally occurring molecules. Thus, most natural products bear indole fragments substituted at C3, e.g. tryptamine and its derivatives. Nature can modify tryptophans *via* oxidative C2 functionalisation and subsequent cleavage of the *N*-heterocyclic ring (Scheme 14). [74,75] Tryptophan 2,3-dioxygenase and indoleamine 2,3-dioxygenase are heme-containing enzymes responsible for the oxidative cleavage of tryptophan along the kynurenine pathway.

Scheme 14: Oxidative C2 functionalisation of tryptophan in Nature.



The naturally occurring duocarmycins and several drug molecules were isolated from *Streptomyces* bacteria, and show very high cytotoxicity[76] that is exploited in the treatment of cancerous cells and arises from DNA alkylation (Figure 3)[77]. Additional synthetic duocarmycins have shown enhanced absorbance and signs of remision in patients.[78] Isomeridianin G belongs to the family of meridianins, which inhibit protein kinases;[79] synthetic analogues show promise as GSK-3 inhibitors.[80] The natural product angustilobine B was first isolated from *Alstonia angustiloba*[81] and more recently from *Alstonia scholaris.*[82] Atevirdine has been identified as a reverse transcriptase inhibitor for the treatment of HIV.[83,84]

Figure 3: Naturally occurring C2-functionalised *N*-unprotected indoles.



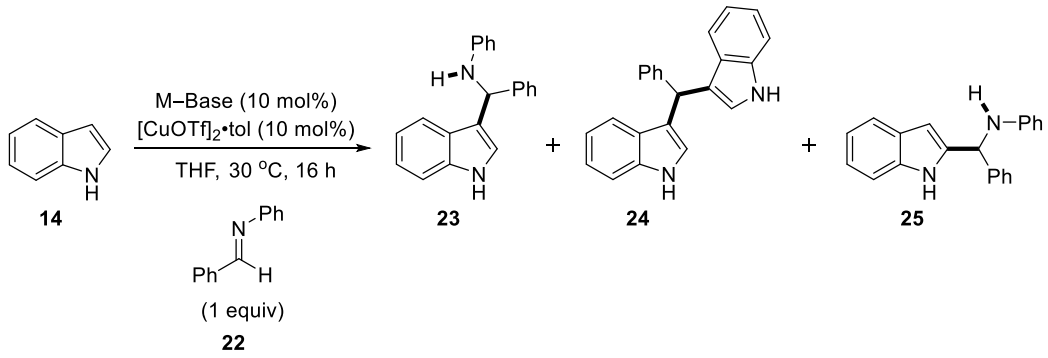
While we are able to negate the requirement for a protecting group for C2 functionalisations the selectivities observed with our system (though promising (1:1)) were not synthetically useful.

1.5 Optimisation of the Catalyst System

1.5.1 Optimisation of the Brønsted Base Component

So far, the best result in terms of both reactivity and C2 selectivity was obtained using K–HMDS and copper(I) triflate as a catalyst system (Table 3, entry 1). However, strong amide bases may hamper a good functional group tolerance in the substrate scope. Thus, various weaker potassium bases were screened under otherwise identical conditions (Table 3, entries 2–4). Gratifyingly, the intended C2 product was still observed when decreasing the basicity of the potassium catalysts; the carbonate catalyst was chosen to further optimise the system (Table 3, entries 5–9). A slight increase in the selectivity of the C2 product was observed in the presence of lithium carbonate over other tested carbonates (Table 3, entry 5). Thus, lithium carbonate was used as a more convenient Brønsted base catalyst in subsequent experiments. The catalytic use of metal carbonates in organic synthesis has been reported, but few examples of intermolecular C–C bond formations exist. Potassium carbonate has been used for the cyanosilylation of aldehydes and ketones.[85] Caesium carbonate has been used in several transformations; notable the formylation and methylation of amines with CO_2.[86-90] Silver carbonate sp σ-coordination has been used for the synthesis of pyrroles[89-91] and structurally diverse heterocycles[92] as well as activation of silicon pronucleophiles[93].

Table 3: Influence of a weaker base on both reactivity and C2 selectivity.[a]



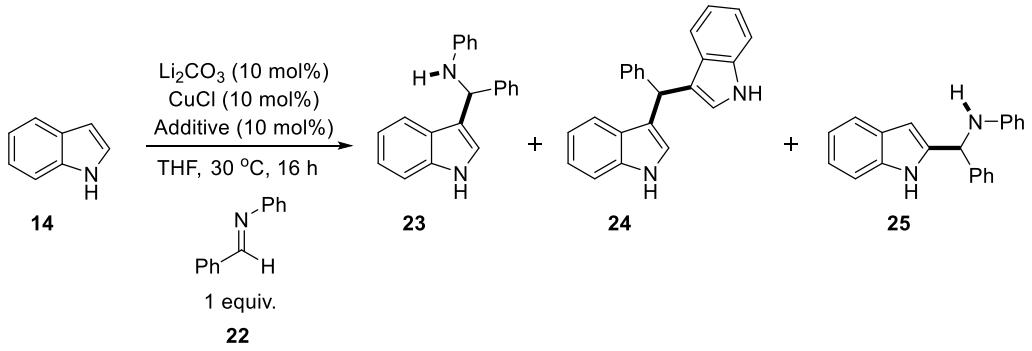
Entry	M–base	yield (%)[a]	selectivity 25:C3 [23:24][a]
1	KHMDS	60	1.2:1 (1:>99)
2	KO^{t}Bu	60	1.4:1 (1:>99)
3	KOAc	78	1.5:1 (1:>99)
4	K_2CO_3	78	1.5:1 (1:>99)
5	Li_2CO_3	77	2.0:1 (1:>99)
6	Na_2CO_3	63	1.4:1 (1:>99)
7	$CaCO_3$	56	1:1.4 (1:>99)
8	$SrCO_3$	56	1:1.6 (1:>99)
9	Ag_2CO_3	28	1:1.5 (1:>99)

[a] Both NMR yield and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard.

1.5.2 Optimisation of the Lewis Acid's Counteranion

Next, the effect of the counteranion in the Lewis acidic copper(I) salt was investigated (Table 4). Thus, prior to the catalytic C–C bond formation a metathesis reaction was carried out at 25 °C for 1 h between copper(I) chloride and a variety of sodium or silver salts bearing weakly coordinating counteranions [*in situ* generation of a more Lewis acidic copper(I) salt]. Such reactions are well documented in the literature.[94] When copper(I) chloride and lithium carbonate were used as the catalyst system, selectivity for the C2 product was 2:1 (Table 4, entry 1). In case of silver co-catalysts, selectivities remained essentially unchanged (entries 2–5). On the other hand, the use of sodium salts proved to be more effective (entries 6–9); among these, sodium tetrafluoroborate was found to be the best mediator giving the intended C2 product in a 7.8:1 ratio, albeit in low yield (entry 7).

Table 4: Influence of the counteranion on both reactivity and selectivity.



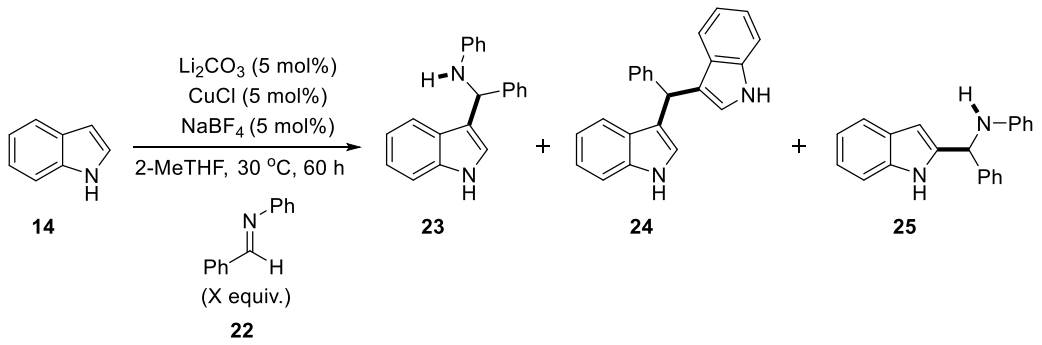
entry	additive	yield (%)[a]	selectivity C2:C3 [C3:bis(C3)][a]
1	none	77	2:1 (1:>99)
2	AgOTf	56	2.0:1 (1:>99)
3	$AgBF_4$	37	2.0:1 (1:>99)
4	$AgPF_6$	59	2.0:1 (1:>99)
5	$AgSbF_6$	58	1.7:1 (1:>99)
6	NaOTf	NR[b]	–
7	$NaBF_4$	34	7.8:1 (1:>99)
8	$NaPF_6$	10	2.8:1 (1:>99)
9	$NaSbF_6$	79	4.2:1 (1:>99)

[a] Both NMR yield and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard. Catalyst components were pre-stirred at 25 °C for 1 h. [b] A reaction was not observed; only starting materials were detectable.

1.5.3 Optimisation of the Substrate Ratio

Next, the indole-to-imine ratio was investigated. Indeed, it was found earlier that gradual addition of the indole over 15 h to a solution of the pre-stirred catalyst components, in the presence of the imine, gave a higher C2 selectivity than the reverse addition over the same period; these data suggested that a higher local concentration of the imine increased the C2 selectivity. In turn, the effect of the imine equivalents (0.5–2.5 equiv), relative to the amount of indole, on both reactivity and C2 selectivity was investigated (Table 5). First, it was found that the use of 2-methyl-THF was beneficial to both NMR yield and regioselectivity (entry 2 vs. entry 1). When less than one equivalent of the imine was used, the C2 selectivity decreased (entries 3 and 4). At two equivalents of imine a maximum was reached where adding additional equivalents began to decrease the C2 selectivity (entries 5–9).

Table 5: Influence of the substrate ratio on both reactivity and selectivity.[a]



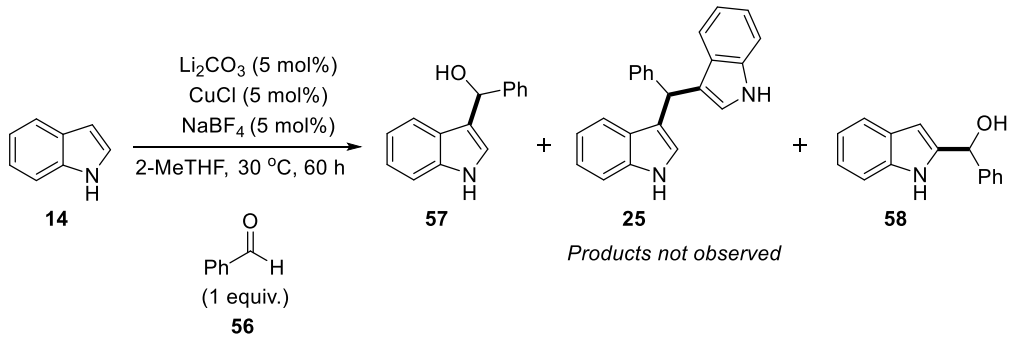
entry	imine equiv	yield (%)[b]	selectivity C2:C3 [C3:bis(C3)][b]
1[c]	1.0	34	7.8:1 (1:>99)
2	1.0	62	12:1 (1:>99)
3	0.5	quant	5.0:1 (1:>99)
4	0.6	quant	5.0:1 (1:>99)
5[d]	1.5	44	16:1 (1:>99)
6	2.0	90	22:1 (1:>99)
7	2.1	88	23:1 (1:>99)
8	2.2	80	23:1 (1:>99)
9[d]	2.5	38	20:1 (1:>99)

[a] Catalyst components were pre-stirred at 25 °C for 1 h. [b] Both NMR yield and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard. [c] THF was used as the solvent. [d] Reaction time: 16 h.

In addition to this C2-selective Mannich-type reaction (using an aldimine as the electrophile), a potentially C2-selective aldol reaction was attempted (using benzaldehyde as the electrophile; Scheme 14). While such transformation would have broadened the scope and provided access to interesting

secondary alcohols, a conversion of the starting materials was not observed even under forcing conditions.

Scheme 15: Attempted potentially C2-selective aldol reaction



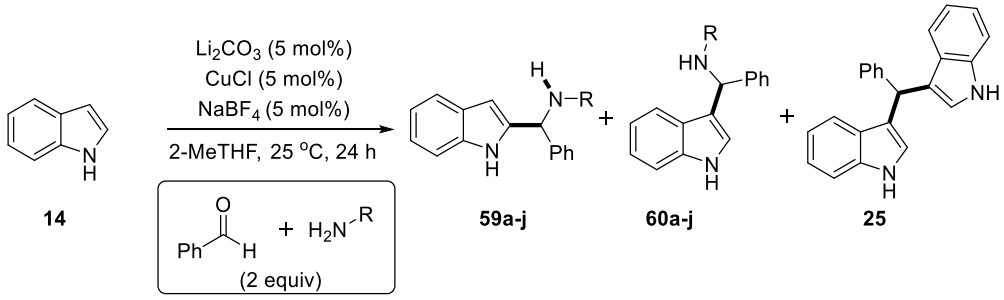
While this result was disappointing, it opened the possibility for the use of classic Mannich conditions, i.e. applying a three-component approach rather than the indole and an isolated imine. Such strategy enables a faster screening of substrates and conditions because the need to prepare and purify imines is not necessary anymore. Moreover, unstable imines could be generated *in situ* and reacted directly without the need for isolation.

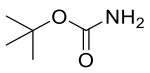
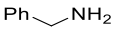
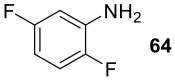
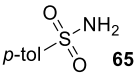
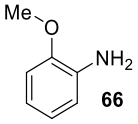
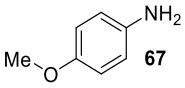
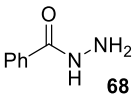
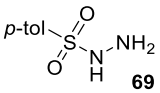
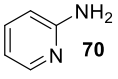
1.6 Investigation of a Three-Component System and Substrate Scope

1.6.1 Initial Examination of a Three-Component System

First, suitable *N*-protecting groups of the primary amine component were screened in order to see their effect on both reactivity and regioselectivity (Table 6). Such information may be important due to the challenging *N*-deprotection of simple aniline-derived imines. No reaction was observed for alkylamino protecting groups such as *tert*-butyl and benzyl (Table 6, entries 2 and 3) as well as aniline; unusual since this worked well as the isolated imine. T*ert*-butoxycarbonyl (boc) protected imines[95] proved unreactive (Table 6, entry 1). Other classic protecting strategies such as tosyl, pmp, hydrazones and hydrazides all failed to achieve reasonable selectivities. Electron withdrawing groups such as fluoride enhanced the selectivity though this did not translate for 2-pyridylamine (Table 6, entry 4 vs 10). *O*-anisidine proved to be very selective for C2 possibly through ortho-complexation with a metal species. This procedure was adopted to rapidly assess substrate tolerance.

Table 6: Screening of *N*-protecting groups for a three-component system.[a]



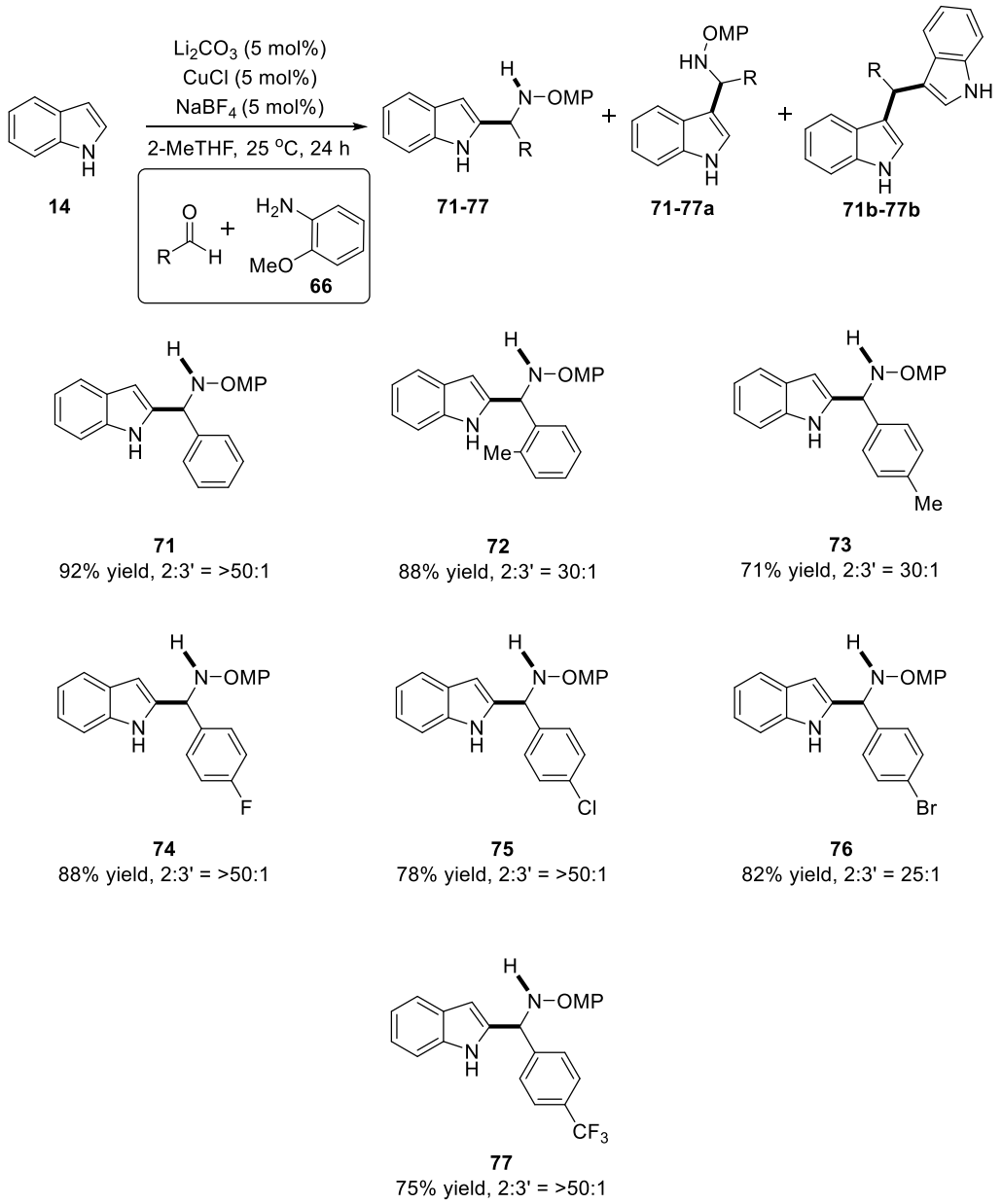
entry	amine	yield (%)[b]	Selectivity C2:C3 [C3:bis(C3)][b]
1	 **61**	NR[c]	–
2	 **62**	NR[c]	–
3	 **63**	NR[c]	–
4	 **64**	47	28:1 (1:>99)
5	 **65**	34	1:16 (1:>99)
6	 **66**	74	>50:1 (1:>99)
7	 **67**	24	1:>99 (1:>99)
8	 **68**	NR[c]	–
9	 **69**	3	1:>99 (2:1)
10	 **70**	45	4:3 (1:2)

[a] Imine components were pre-stirred at 30 °C for 1 h prior to the reaction. Catalyst components were pre-stirred at 25 °C for 1 h. [b] Both NMR yield and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard. [c] A reaction was not observed; only starting materials were detectable.

1.6.2 Examination of the Scope for *N*-OMP-Protected Imines

Under the optimised conditions a range of functionalities were tolerated (Table 7). The use of aromatic aldehydes displaying functional groups in *ortho*-, *meta*-, or *para*-position led to the formation of the corresponding Mannich adducts with C2:C3 ratios ranging from 30:1 to >50:1. Both electron-donating and electron-withdrawing groups proved to be applicable.

Table 7: Screening of aromatic *N*-OMP-protected aldimines.[a]

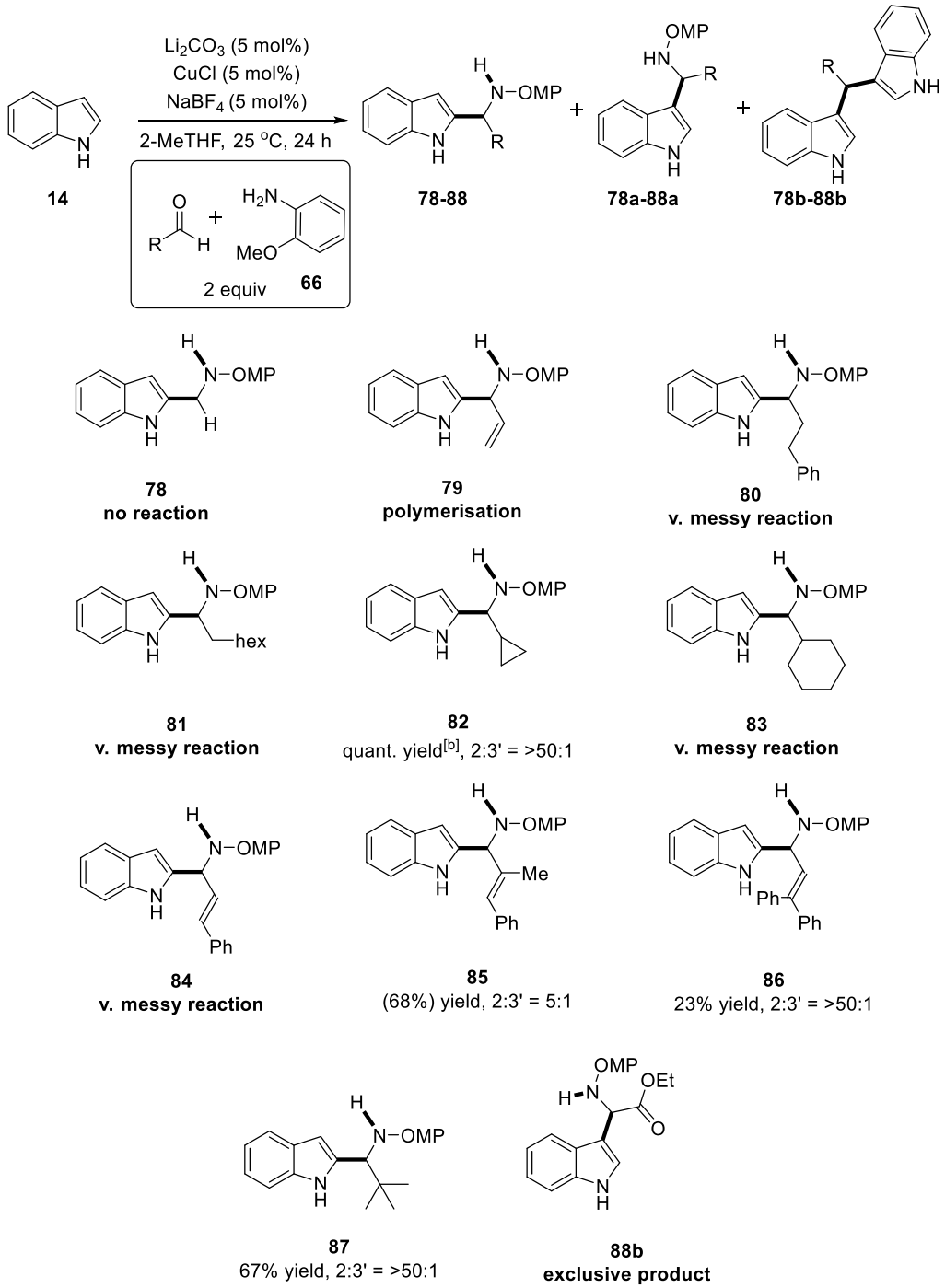


[a] Both NMR yield and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard.

While the scope for aromatic aldehydes was very promising, aliphatic and more "exotic" carbonyl derivatives proved to be challenging substrates under the reaction conditions (Table 8). Several attempts were made to use formaldehyde so to incorporate a simple amino methylene fragment onto indole; solutions of formaldehyde as well as paraformaldehyde did not give any reaction with indole.

Problems were also encountered with primary aliphatic aldehydes, such as octanal and hydrocinnamaldehyde, as well as a secondary aliphatic aldehyde, cyclohexane carbaldehyde. Gratifyingly, cyclopropane carbaldehyde worked well and provided additional useful data regarding the mechanism (*vide infra*). Attempts with Michael acceptors, such as acrolein and cinnamaldehyde, gave polymerisation. This issue could be remedied to some extent by using α-methyl cinnamaldehyde, but the regioselectivity turned out to be poor. Replacing both β-positions with phenyl rings resulted in a highly regioselective transformation. The highly activated glyoxylate resulted in the exclusive formation of the bis(C3) product.

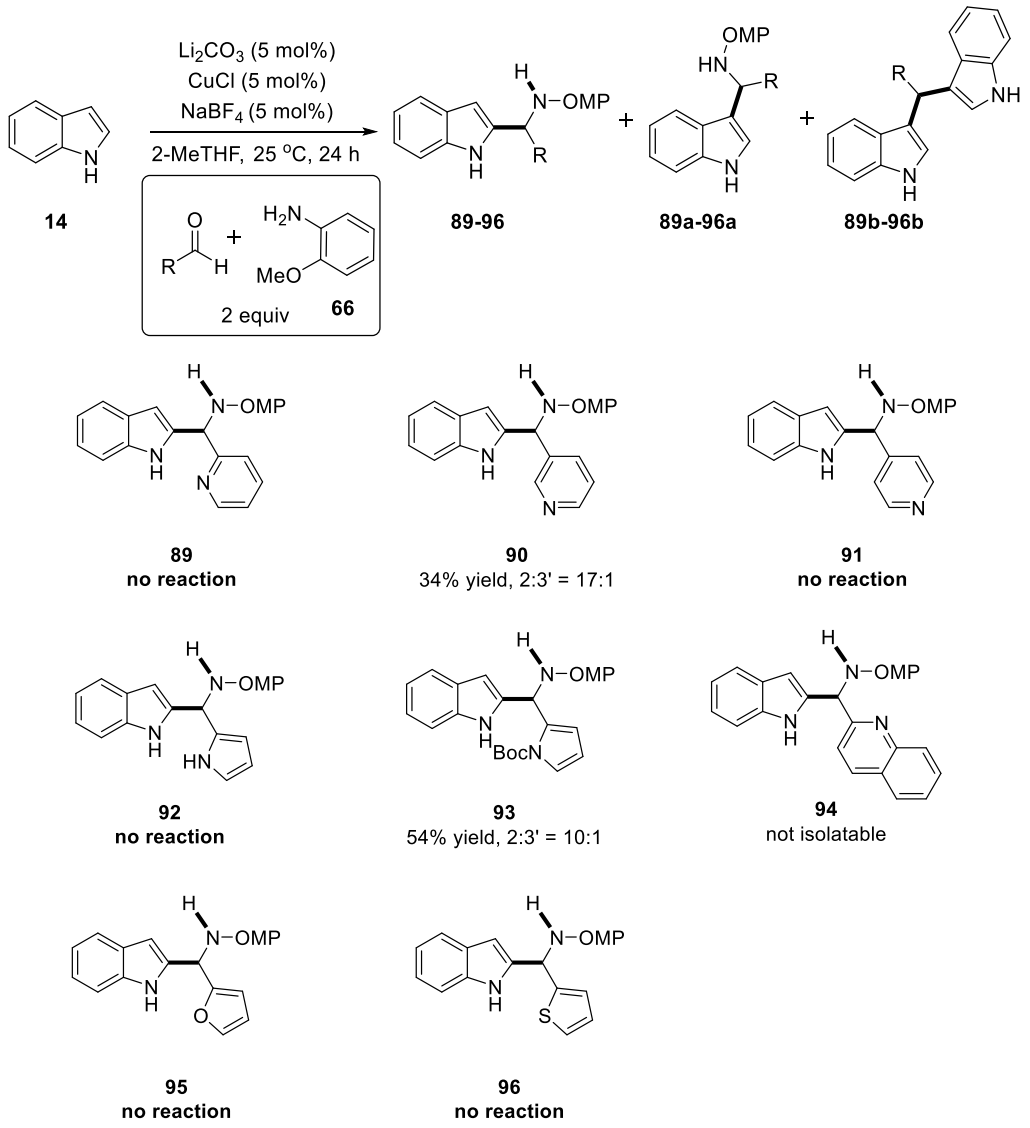
Table 8: Screening of various *N*-OMP-protected aldimines.[a]



[a] Both NMR yield and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard. [b] NMR yield.

In addition, heteroaromatic substrates –as potentially pharmaceutically relevant molecules– were examined (Table 9). Here, the reactivity proved to be less general. For instance, pyridyl groups were tolerated only at C3. While a reaction was not observed with the *N*-unprotected pyrrole derivative, *N*-Boc protection enabled reasonable selectivity and reactivity. Furan and thiophene derivatives also proved to be unreactive towards indole.

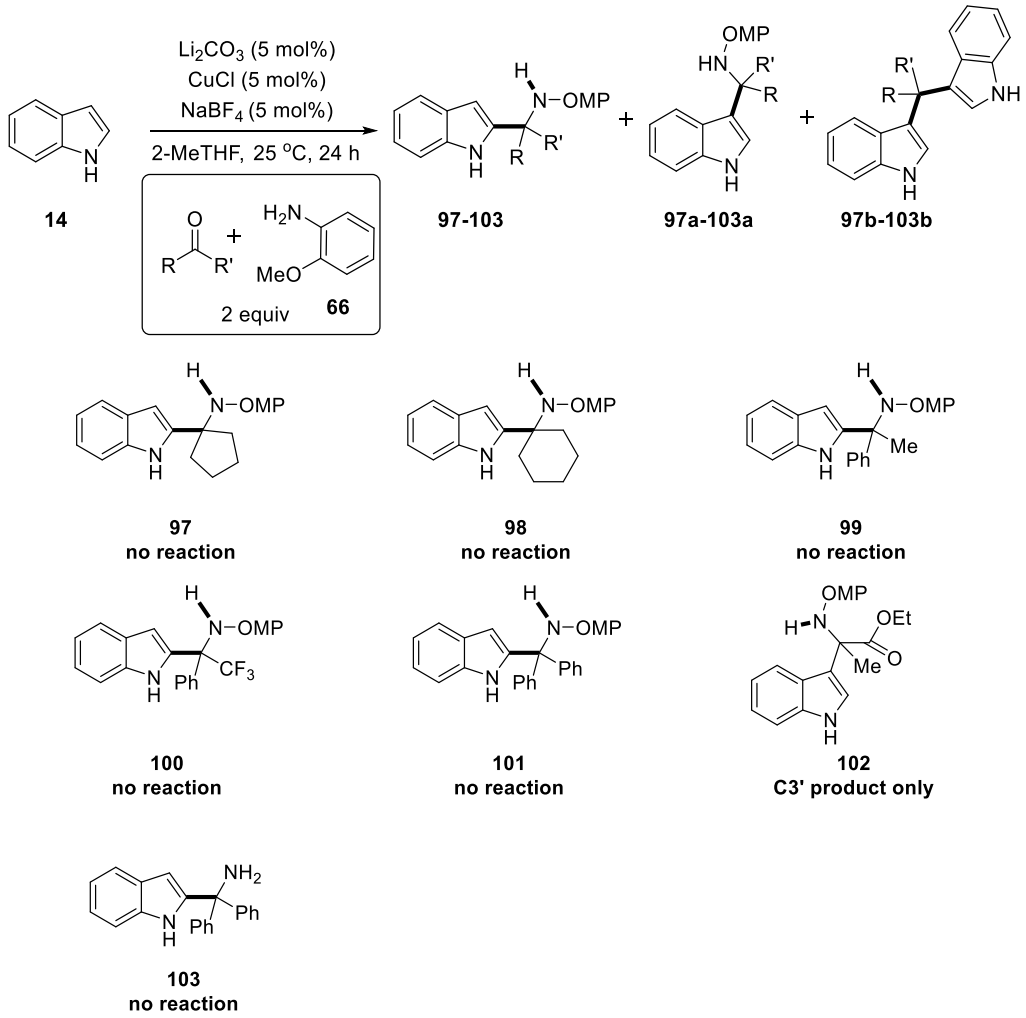
Table 9: Screening of heteroaromatic OMP-protected aldimines.[a]



[a] Both NMR yield and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard. NMR yield compounds not isolated.

Next, ketones were investigated (Table 10). Their reactivity turned out to be poor; a reactivity was not observed with aliphatic, aromatic, and "mixed" ketones. The activated ketone pyruvate gave only overaddition to the *bis*-C3 product while the commercially available benzophenone imine failed to react.

Table 10: Screening of *N*-OMP-protected ketimines.[a]

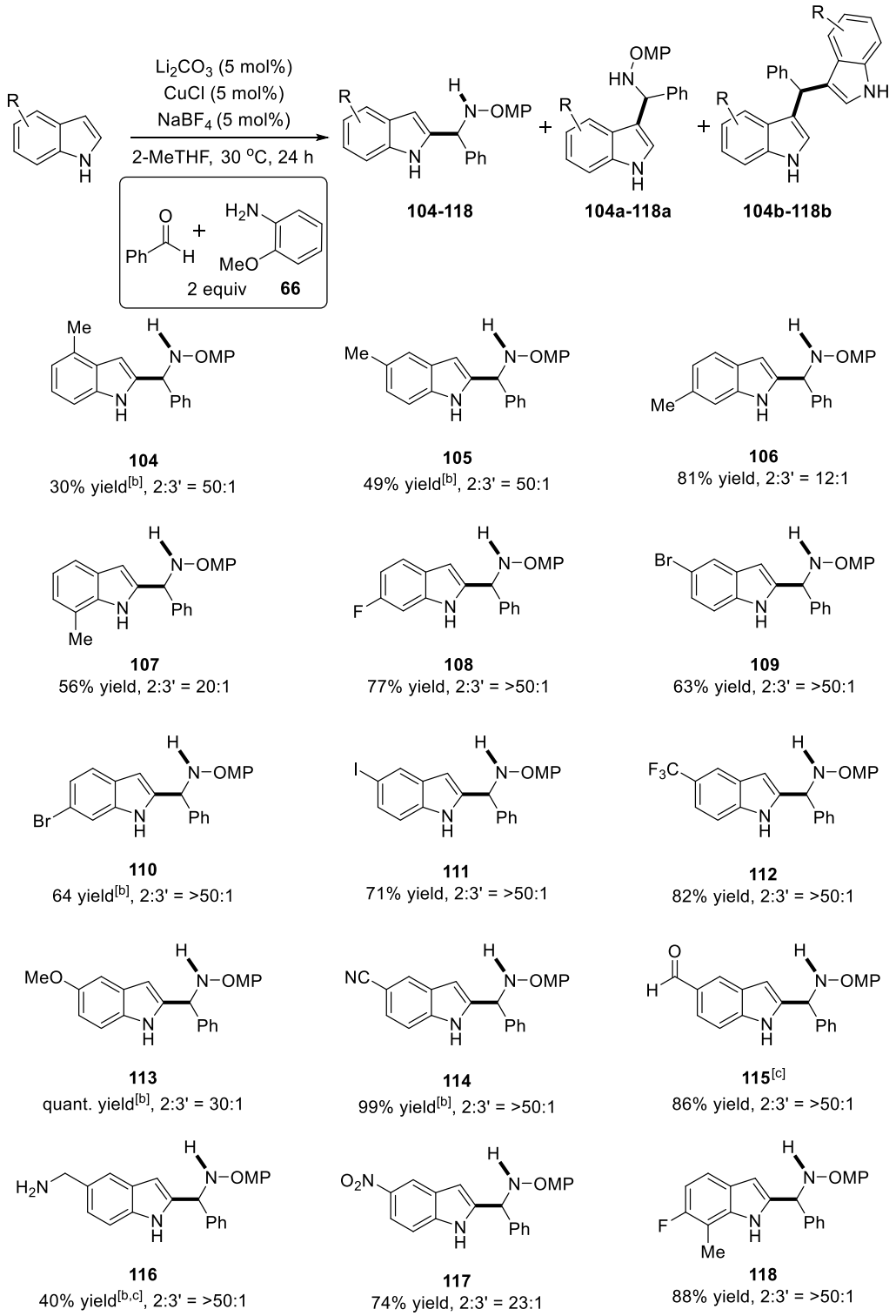


[a] Both NMR yield and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard.

1.6.3 Examination of the Scope for Indoles

Pleasingly, a wide range of functionalised indoles were tolerated under the reaction conditions (Table 11). While the majority of the scope was achieved using C5-substituted indoles, substitution at all positions was shown to be acceptable. In addition to methyl groups, all halogen atoms (F, Cl, Br, I) allowing for further chemical transformations at these synthetic handles. Similarly, both electron-donating and electron-withdrawing groups were tolerated at the indole core. Interestingly, amino and carbonyl groups could be tolerated as long as the imine was pre-formed at 30 ^{o}C for 1 h prior to its addition to the reaction mixture.

Table 11: Screening of ordinary indoles.

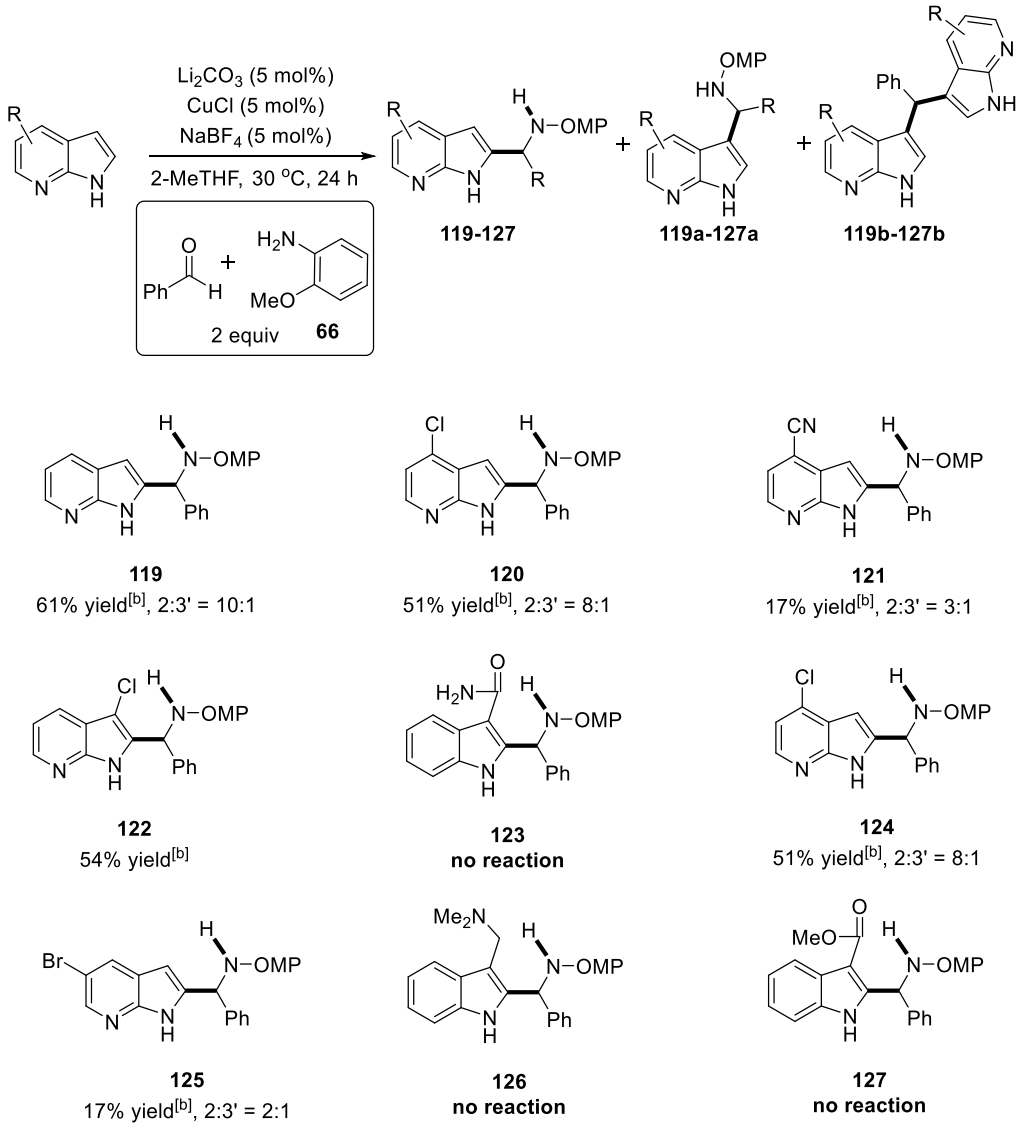


[a] Both NMR yield and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard. [b] NMR yield compound not isolated. [c] Imine components were pre-stirred in half amount of the solvent at 30 °C for 1 h.

Aza-indoles represent interesting substrates, but are encountered sporadically in the scope of indole-exploiting reactions in the literature.[96] In our case, under the optimized conditions a reactivity was observed for a range of different aza-indoles (Table 12). The use of 4-, 5-, and 6-aza-indoles resulted

in a very poor reactivity (<5%); these substrates were not further pursued. The use of some substituted 7-aza-indoles gave moderate reactivity, but the poor regioselectivity made the transformations synthetically less useful. However, good results were obtained by using 3-chloro-7-aza-indole and 5-methoxy-7-aza-indole. The use of several 3-functionalised aza-indoles proved to be unsuccessful.

Table 12: Screening of various aza-indoles.[a]



[a] Both NMR yield and regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard. [b] NMR yield compound not isolated.

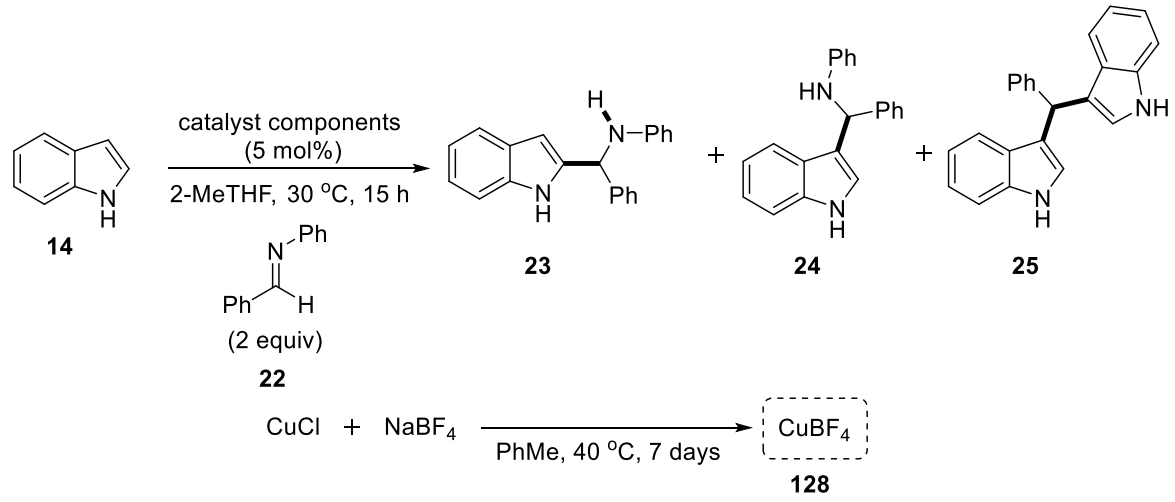
1.7 Investigations Towards the Mechanism of the C2-Selective Mannich

1.7.1 Significance of Individual Catalyst Components

The optimization experiments regarding the most active and selective catalyst revealed that a three-component catalyst system was most effective: CuCl, $NaBF_4$, Li_2CO_3; in a molar ratio 1:1:1. While the presence of all three components proved to be critical for both reactivity and selectivity, we wanted to gain further insight into the identity of the catalytically active species. We hypothesized that copper(I) chloride [Cu(I)Cl] and $NaBF_4$ would undergo an anion metathesis to generate *in situ* $Cu(I)BF_4$. Both reactivity and selectivity for the use of the commercially available $Cu(I)BF_4$•$(MeCN)_4$ in the presence of Li_2CO_3 –under otherwise identical conditions– were found to be disappointing; this poor result may be ascribed to the tightly bound ligand (MeCN) thus blocking coordination sights at the metal center. In order to test such hypothesis and to carry out control experiments, $Cu(I)BF_4$[97] and $Cu(I)_2CO_3$[98] were synthesized according to literature procedures. While literature procedures were followe purity of these compounds was not assayed.

Next, a variety of experiments were carried out with our model transformation at 30 °C for 15 h with preformed imine (Table 13). The use of the "standard three-component Cu(I) system" gave the product in 27% yield with a C2:C3 selectivity of 23:1 (entry 1). In contrast, replacing Cu(I) with Cu(II) led to 47% yield but a substantially decreased C2:C3 selectivity (3.8:1; entre 2). Gratifyingly, the use of the synthesized solvent-free $Cu(I)BF_4$ gave the product in 67% yield with a C2:C3 selectivity of 24:1 (entry 3). Interestingly, when the anions were swapped here, the yield dropped but the selectivity remained similar (entry 4); this outcome could be explained by a distinct rate of anion metathesis leading to a lower catalyst loading in this particular case. Overall, these experiments confirmed the critical presence of copper(I) for a high C2-selectivity. The significance of lithium was then confirmed through using the synthesized solvent-free $Cu(I)BF_4$ in combination with various other metal carbonates (Na, K, Cs; entries 5–7). While the product yields proved to be similar to the case of Li (entry 3), the selectivity dropped badly (entries 5–7). Interestingly, when the synthesized $Cu(I)_2CO_3$ was used as a sole catalyst, a reaction did not occur at all (entry 8). Overall, these experiments confirmed the critical presence of lithium for a high C2-selectivity. Finally, a control experiment was carried out using the combination of synthesized solvent-free $Cu(I)BF_4$ and $LiBF_4$; here, the reaction proceeded smoothly but the C2:C3 selectivity was inversed (1:2.0; entry 9). This experiment confirmed the critical presence of carbonate for a high C2-selectivity. Overall, we propose a double anion metathesis starting from all three components leading to a mixed Cu(I)/Li carbonate, which may be the active metal–base catalyst for C2–H bond activation of the *N*-unprotected indole. Efforts are ongoing to synthesize, isolate, and characterize the crucial mixed metal salt.

Table 13: Control experiments towards the elucidation of the catalytically active species.



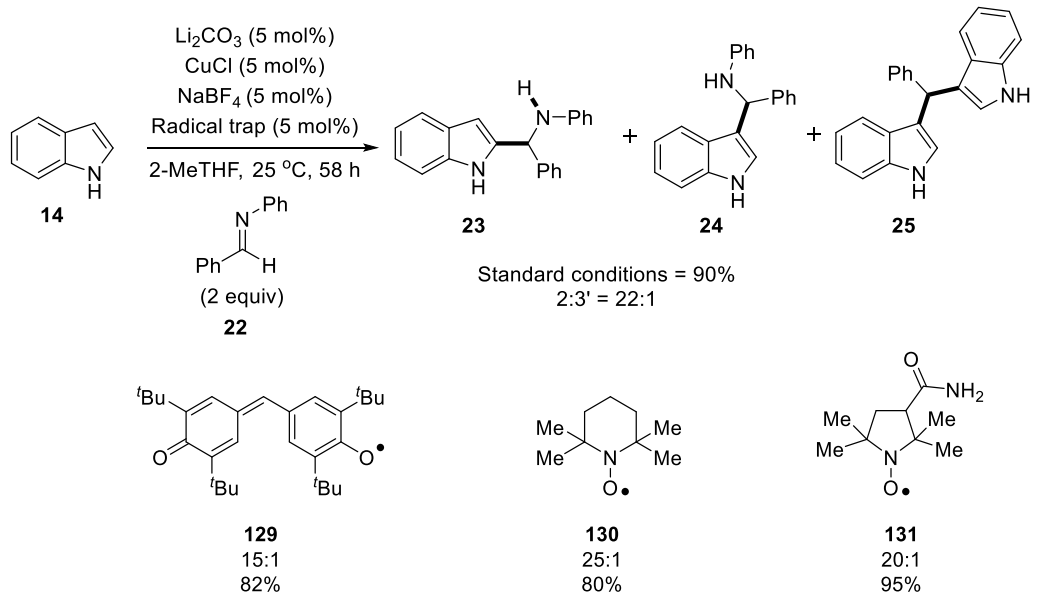
Entry	catalyst components[a]	yield (%)[b]	Selectivity C2:C3 [C3:bis(C3)][b]
	Significance of copper(I)		
1	$CuCl + NaBF_4 + Li_2CO_3$	27	23:1 (1:>99)
2	$CuCl_2 + NaBF_4 + Li_2CO_3$	47	3.8:1 (1:>99)
3	$CuBF_4 + Li_2CO_3$	67	24:1 (1:>99)
4	$LiBF_4 + Cu_2CO_3$	10	20:1 (1:>99)
	Significance of lithium		
5	$CuBF_4 + Na_2CO_3$	51	7.0:1 (1:>99)
6	$CuBF_4 + K_2CO_3$	65	4.0:1 (1:>99)
7	$CuBF_4 + Cs_2CO_3$	61	2.0:1 (1:>99)
8	Cu_2CO_3	NR	–
	Significance of carbonate		
9	$CuBF_4 + LiBF_4$	58	1:2.0 (1:>99)

[a] Catalyst components prestirred for 1 h at 30 °C prior to use. [b] Both NMR yield and regioselectivity were determined by ^1H NMR spectroscopic analysis of an aliquot of the reaction mixture using dibenzyl ether (0.25 M in mesitylene) as an internal standard.

1.7.2 Examination of a Potential Radical Reaction Pathway

When considering plausible mechanistic pathways for the C2 functionalisation of the *N*-unprotected indole core, a radical mechanism may seem conceivable based on the reagents and catalyst components used. In addition to the proposed ionic mechanism[99] for Grubbs' silylation of *N*-heterocycles, a radical pathway has been also described.[100] Thus, we examined the use of three commercially available radicals –galvinoxy (**129**), TEMPO (**130**), *and* 3-carbamoyl-PROXYL (**131**)– as additives in our standard transformation; however, the imine was used directly here (Scheme 16). Their use resulted only in a minor erosion to the normal selectivity observed. Thus, while the use of stable radicals may give some hint that the reaction does not proceed *via* a radical pathway, it is not conclusive. Indeed, *in situ*-formed radicals may have reacted preferentially with the substrates as these were present in higher concentration. Also, the free radicals may have served as ligands to metal species in solution. Experiments may have to be carried out again in a different setting (different free radicals, higher concentration etc.), and potentially to isolate adducts with these free radicals incorporated.

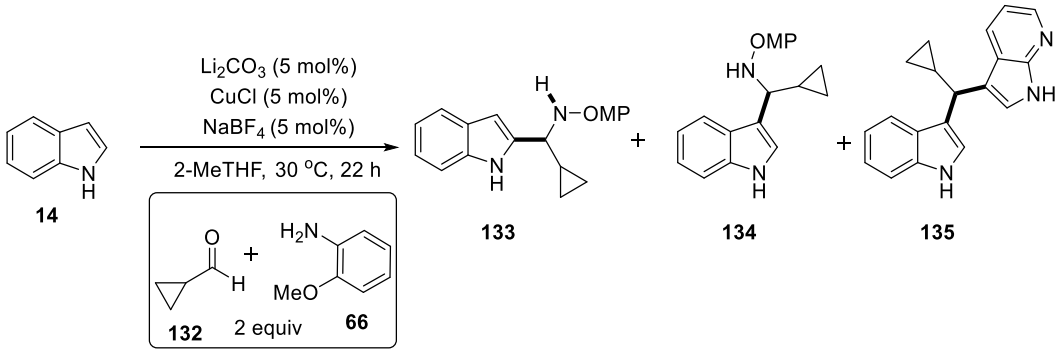
Scheme 16: Use of a variety of radical traps in the model reaction.[a]



[a] The yield and the regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene. Catalyst components were prestirred for 1 h at 25 °C.

With the aim to test the "radical" hypothesis from a different aspect, cyclopropyl carbaldehyde –as a radical clock[101] substrate– was used under under standard conditions. This reaction afforded product **133** selectively in quantitative yield based on the internal standard (dibenzyl ether); however, its isolation proved treacherous. Ring-opened products could not be detected in the ^{1}H NMR spectroscopic analysis of a reaction aliquot.

Scheme 17: Use of cyclopropyl carbaldehyde as a radical clock substrate.[a]

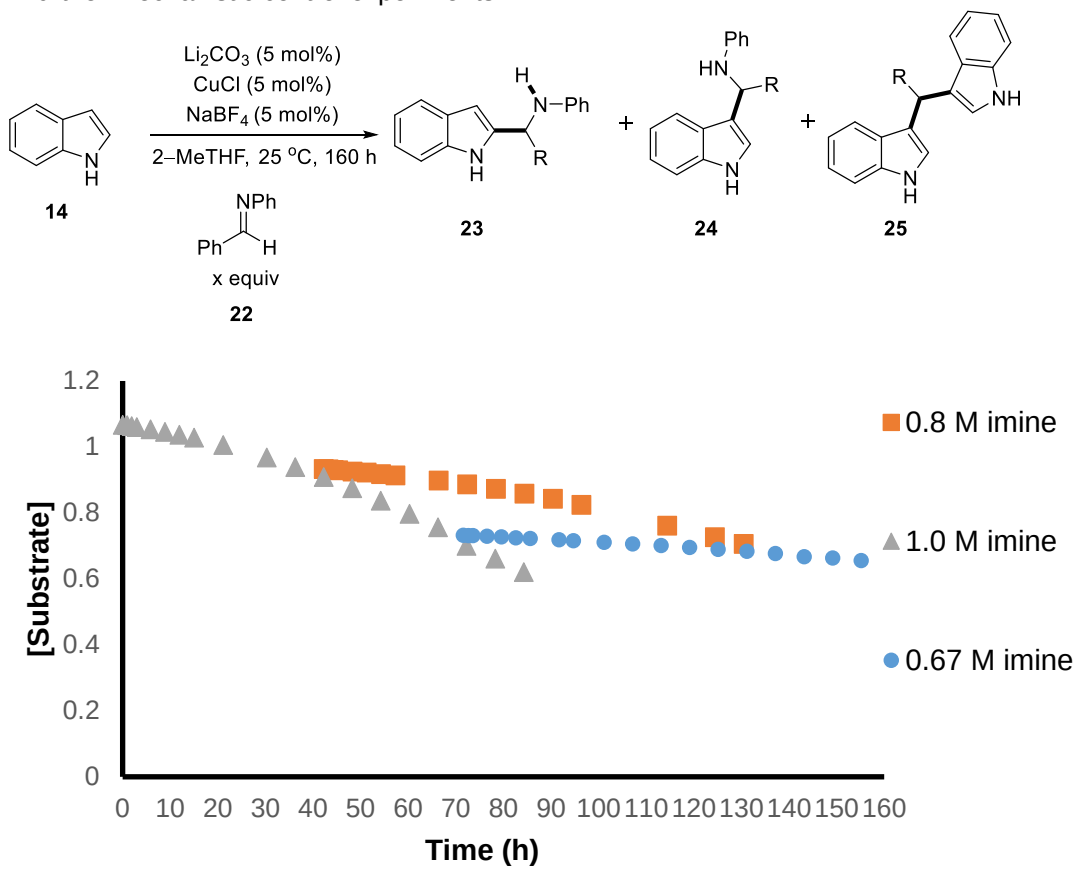


[a] The yield and the regioselectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene.

The studies by Blackmond *et al.* towards reaction progress kinetic analysis has aided in the identification of reaction mechanisms for several different reactions.[102-104] For example the use of kinetic analysis has been applied to the study of several palladium catalaysed transformations. The benefit of the approach being the generation of a wealth of valuable data from a minimum of experiments[102]. This approach[105] was applied to the present C2-selective indole Mannich-type coupling (Chart 1).

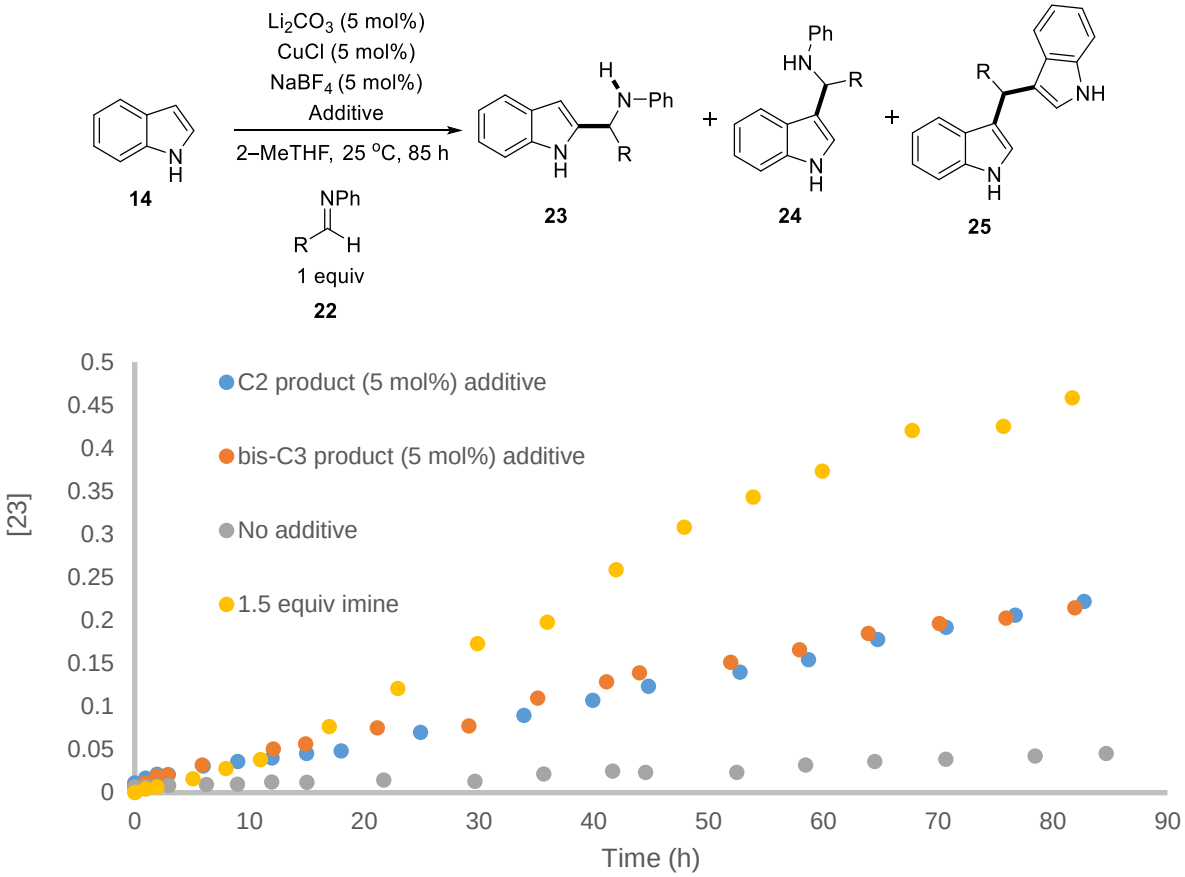
The reaction was run at several different concentrations of the imine **22** keeping the same excess of this reagent in all experiments. This allows the influence of several effects to be observed. Using NMR the concentration of starting material and product was monitored. The concentration of **22** was plotted with respect to the reaction time. This plot was then “time adjusted”; the lower concentrations were overlaid at the time point when they met the highest concentration. Between these reactions the concentration of the substrate is the same but in two cases the reaction has been on for longer allowing products to form and catalsyts to potentially decompose. Since the reaction was effectively at the same time the plots should overlay assuming that there is no product inhibition or catalyst deactivation. Despite the substrate concentration being the same at these points, the reaction rate was notably different. These data highlight the influence of product interaction and catalyst inhibition on the kinetics. Further experiments were cariied out to see if which of these processes was occurring.

Chart 1: Further mechanistic control experiments.



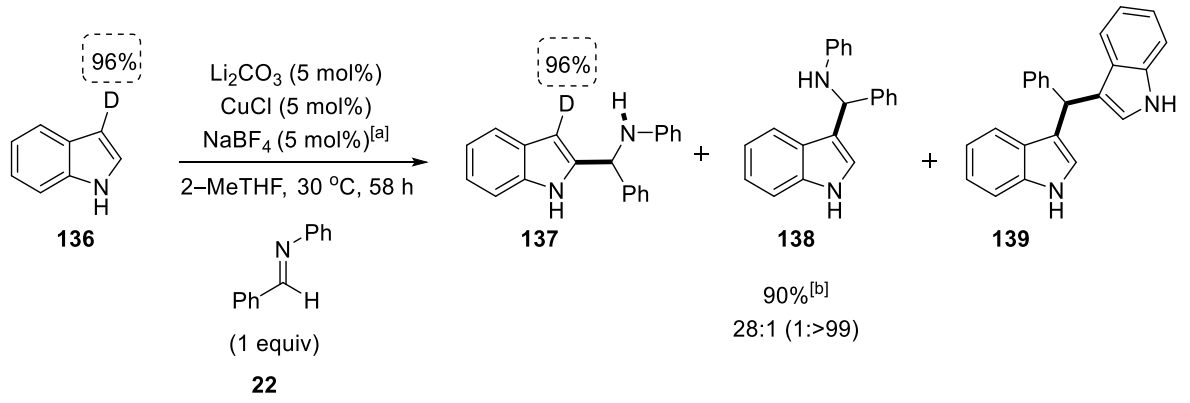
In order to see if the products inhibited the reaction, the isolated products **23** and **24** were added to the catalyst pre-stirring prior to starting the reaction. In order to avoid saturation of the catalyst only one equivalent of imine **22** was added. For both the **23** and **24** additive there was an enhancement in the reaction rate suggesting a ligand-stabilizing influence of the corresponding substrate. The addition of 1.5 equivalents of imine **22** afforded a significant enhancement of the C2 regioselectivity. These data show promise for the addition of a chiral ligand to the system in view of asymmetric catalysis. While several different ligand classes were screend no *ee* was observed. This was demonstrated earlier with the slow addition experimets. While the same excess and additive experiments provided nice data with regards to catalyst deactivation and/or product inhibition, more data was required before a reliable mechanism could be proposed.

Chart 2: Influence of additives on the reaction rate.



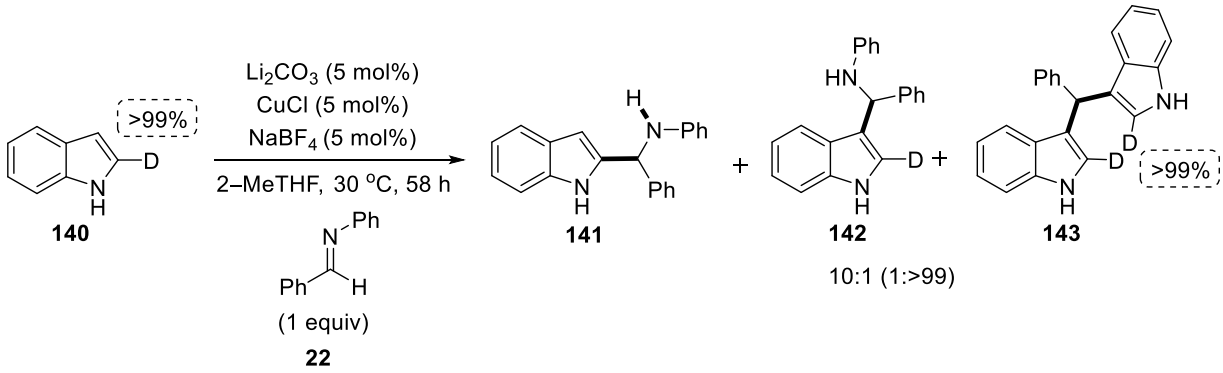
Deuterium labelling experiments were performed using indole deuterated at C3 and C2, respectively. There have been several reports of indole C2 functionalisation *via* a C3-to-C2 migration.[106] By using a C3-deuterated indole we would expect a decrease in the level of deuteration at C3 via an exchange process. The synthesis of this substrate takes advantage of the enamine to use a deuterated DCl catalyst in D_2O to equilibrate to the C3-deuterated product. For the use of the C3-deuterated indole under the normal reaction conditions, a scrambling of the deuterium label was not observed (Scheme 17). This result may suggest that such migration did not occur in our reaction system. For the use of the C2-deuterated indole, the monitoring with time of the labelled substrate vs. "normal" indole gave a small primary kinetic isotope effect (KIE) of 1.54 (Scheme 18). This result may suggest that the C2–H bond activation corresponds to the rate-determining step. Future expeeiments may include monitoring the C3-deutereated indole vs "normal" substrate to see if any minor isotope effect exists. Current work is ongoing to assess the three-component reaction with the same approaches.

Scheme 18: Deuterium labelling experiments: use of indole deuterated at C3.



[a] Catalyst components were prestirred for 1 h at 30 °C. [b] The yield and the geometric selectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene.

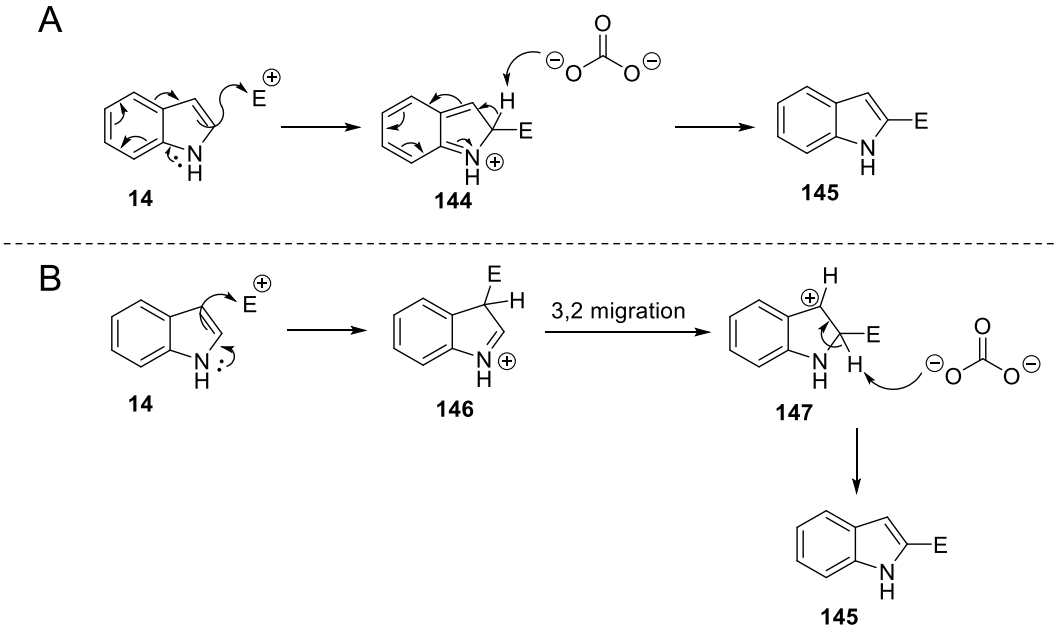
Scheme 19: Deuterium labelling experiments: use of indole deuterated at C2.



[a] Catalyst components were prestirred for 1 h at 30 °C. [b] The yield and the geometric selectivity were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene.

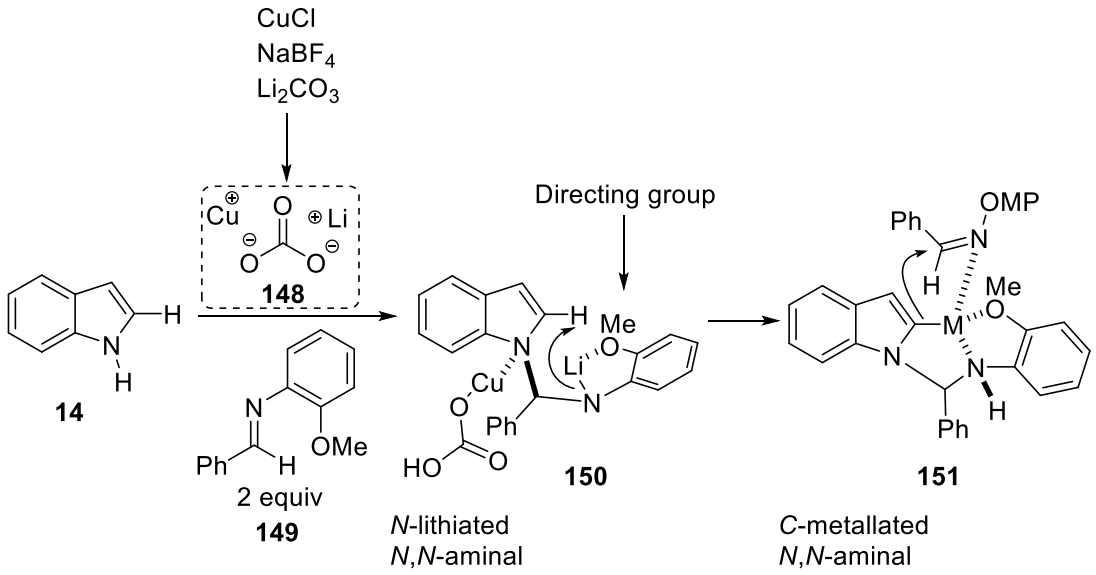
Several different mechanisms can be proposed for this activation. While electrophilic aromatic substitution can proceed via the C2 possition (Scheme 20, A) the unfavourable dearomatisation **144** vs the enamine reactivity through C3 suggests this is unlikely. A more likely scenario is reaction through the enamine to C3 **146** followed by migration **147** (Scheme 20, B). Via this mechanism it would be expected that deuteration at C3 would lead to scrambling at this position. As this was not observed pathway B is also unlikely.

Scheme 20: Plausible mechanisms of C2 alkylation.



Based on these experiments, a C2–H bond activation pathway can be proposed for this C2-selective indole–Mannich-type coupling (Scheme 21). The formation of a heterobimetallic carbonate (Cu/Li) **148** has been suggested. This species may be apt –through coordination to the metal sites– for initial deprotonative N–H bond activation of indole; the resulting metallated enamide would then react at the *N*-terminus with the imine (1 equiv) to form an *N*-lithiated *N*,*N*-hemiaminal **150**; this intermediate corresponds to a lithium amide species, which receives support from the proximal aromatic methoxy group (bidentate coordination). Such a metal–base should be reactive enough to activate the adjacent C2–H bond of indole (deprotonation). The *in situ*-generated *C*-metallated *N*,*N*-hemiaminal **151** would then add to another molecule of the imine (second equivalent; C–C bond formation). The product thus formed would undergo collapse of the hemiaminal moiety to regenerate the original N–H bond of the indole core. This mechanism would correspond to a traceless protecting/directing group approach. Efforts to synthesize, isolate, and independently use such indole-derived *N*,*N*-hemiaminal are on-going.

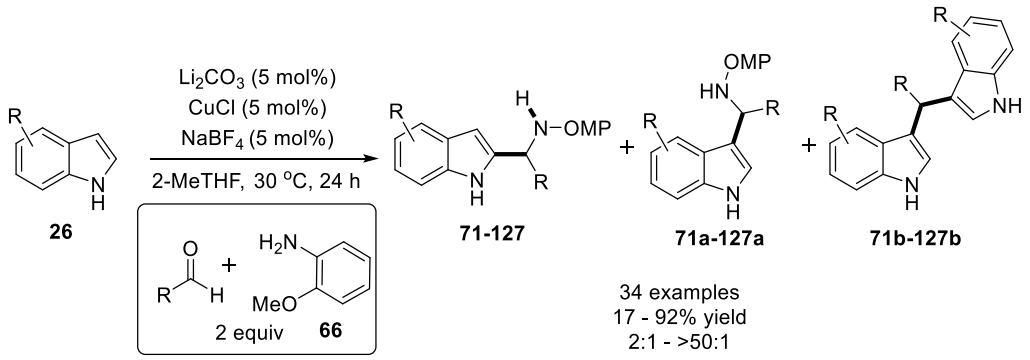
Scheme 21: Proposed C2–H bond activation by a postulated heterobimetallic carbonate.



1.8 Conclusions and Future Work

A rare C2 functionalisation of *N*-unprotected indoles has been reported. This Mannich-type reaction was discovered by serendipity and optimized further. Good to excellent C2-selectivities were achieved, and a mild catalyst system allowed a range of functional groups to be retained through the transformation. The reaction was tolerant of several reactive functional groups, e.g. aldehydes, bromides etc. In an attempt to expand the substrate scope, aldehydes were used without success. This "negative" result opened the possibility of a three-component reaction. Using *o*-anisidine this transformation proceeded smoothly. Mechanistic investigations suggested the formation of a heterobimetallic carbonate through double anion metathesis, and a deprotonative C2–H bond activation by an intermediary lithiated *N*,*N*-hemiaminal, which may serve as a traceless protecting/directing group.

Scheme 22: C2 Specific Mannich Reaction.



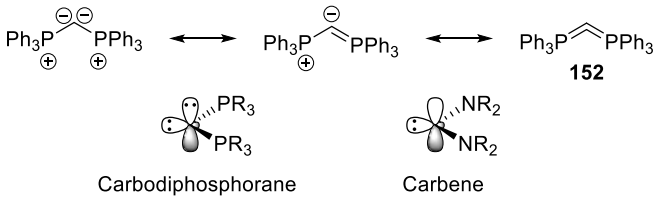
Future work will focus on further exploring the mechanism of this three-component reaction system. Additionally, the use of other *N*-based electrophiles, e.g. aziridines, may be used to form C2-analogues of tryptamines.

2 Catalysis with a carbodicarbene

2.1 Carbenes [Carbon(II)] vs. Carbones [Carbon(0)]

Carbenes, particularly *N*-heterocyclic carbenes (NHCs), have been established arguably among the most common Lewis base catalysts and ligands (Scheme 23; right).[107] These species represent carbon in its formal oxidation state (II); they possess a vacant p orbital and a lone pair of electrons in an sp^2 orbital. In contrast, so-called carbones are carbon species with the central atom in a formal oxidation state (0); thus, while such compounds are neutral they possess two lone pairs of electrons and no vacant orbital at carbon (Scheme 23; left).[108] Among the first examples reported in the late 1960s are so-called carbodiphosphoranes (CDPs). Their strongly basic nature has been demonstrated in their extraordinary first proton affinity (280 $kJmol^{-1}$; vs. 250 $kJmol^{-1}$ for carbenes), and moreover a high second proton affinity of 186 $kJmol^{-1}$ indicating a substantial dibasic character.[109] A variety of carbones have been reported; according to the substituents at the central carbon atom the following classes may be distinguished: **allenes or heterocumulenes,** [110-117] **carbodicarbenes**[118-128] and CDPs[129-137].

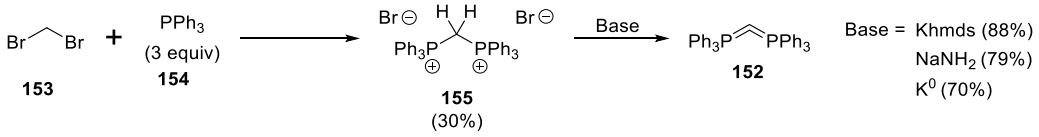
Scheme 23: Carbon in its oxidation states (II) and (0): carbenes and carbones.



3.2 Synthesis of a Carbodiphosphorane

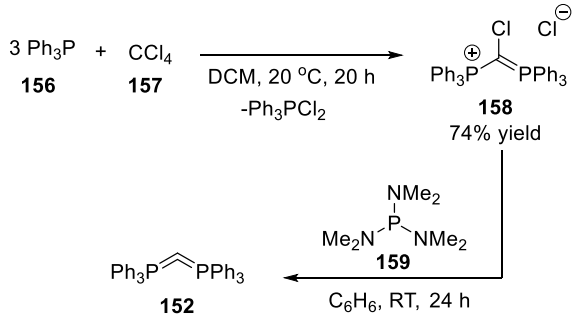
The first reported synthesis of hexaphenylcarbodiphosphorane (**152**) was achieved through reaction of dibromomethane with an excess of triphenylphosphine forming an intermediary bis(phosphonium) bromide salt that was deprotonated using potassium metal (Scheme 24).[138] Other bases used include K–HMDS[139] and Na–NH_2.[140]

Scheme 24: First reported synthesis of carbodiphosphorane **152** (CDP).



After this initial low-yielding route, a new method was developed by Appel *et al.* (Scheme 25).[141] The sequence included double nucleophilic substitution on CCl_4 using an excess of triphenylphosphine, and subsequent dechlorination by tris(dimethylamino)phosphine.

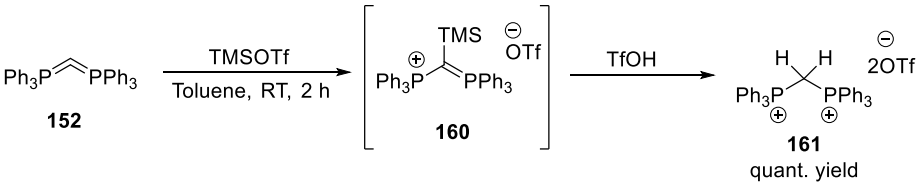
Scheme 25: Synthesis of the CDP precursor salt.



2.3 Stoichiometric Reactivity of a Carbodiphosphorane

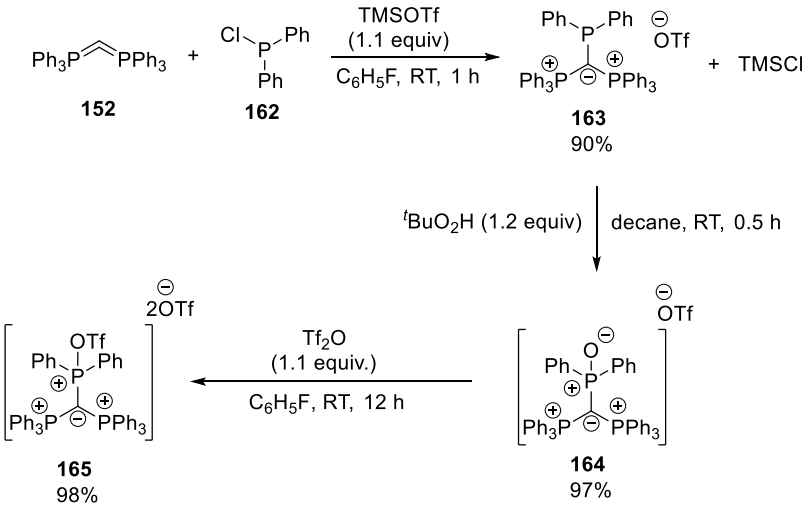
Hexaphenylcarbodiphosphorane, abbreviated in the following by CDP, has been explored in a variety of contexts. Its addition to an equimolar amount of TMSOTf afforded the corresponding silyl-complex **160** as an air-sensitive complex which was unstable in solution (Scheme 26). Subsequent reaction of the latter with triflic acid afforded –after elimination of the TMS moiety– the bis(protonated) CDP complex rather than the (presumably) unstable protonated silyl-complex; this "decomposition" was indicated by ^{31}P NMR spectroscopy (26.2 ppm –> 20.0 ppm).[142]

Scheme 26: Stoichiometric reactivity of a carbodiphosphorane towards a silicon Lewis acid.



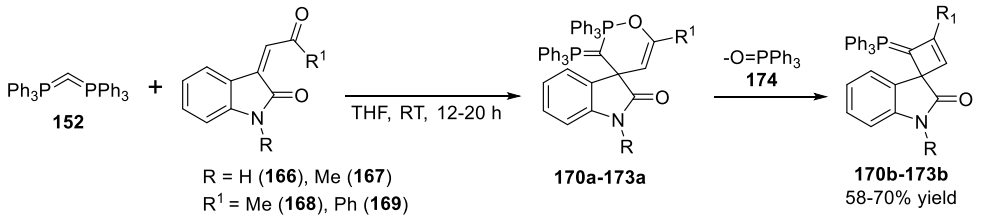
In the presence of a stoichiometric amount of TMSOTf, CDP was also shown to react with a chlorophosphine through nucleophilic substitution (Scheme 27). Addition to the phosphonium center forms novel halo and *pseudo*halophosphonium dications **163**.[143] Oxidation of this complex with *tert*butylperoxide affords the unstable trication **164** which was stabilised by triflation of the phosphine oxide forming **165**. A similar synthetic strategy is utilized for C–F activation using transient phosphonium dications.[144]

Scheme 27: Stoichiometric reactivity of a carbodiphosphorane towards a chlorophosphine.



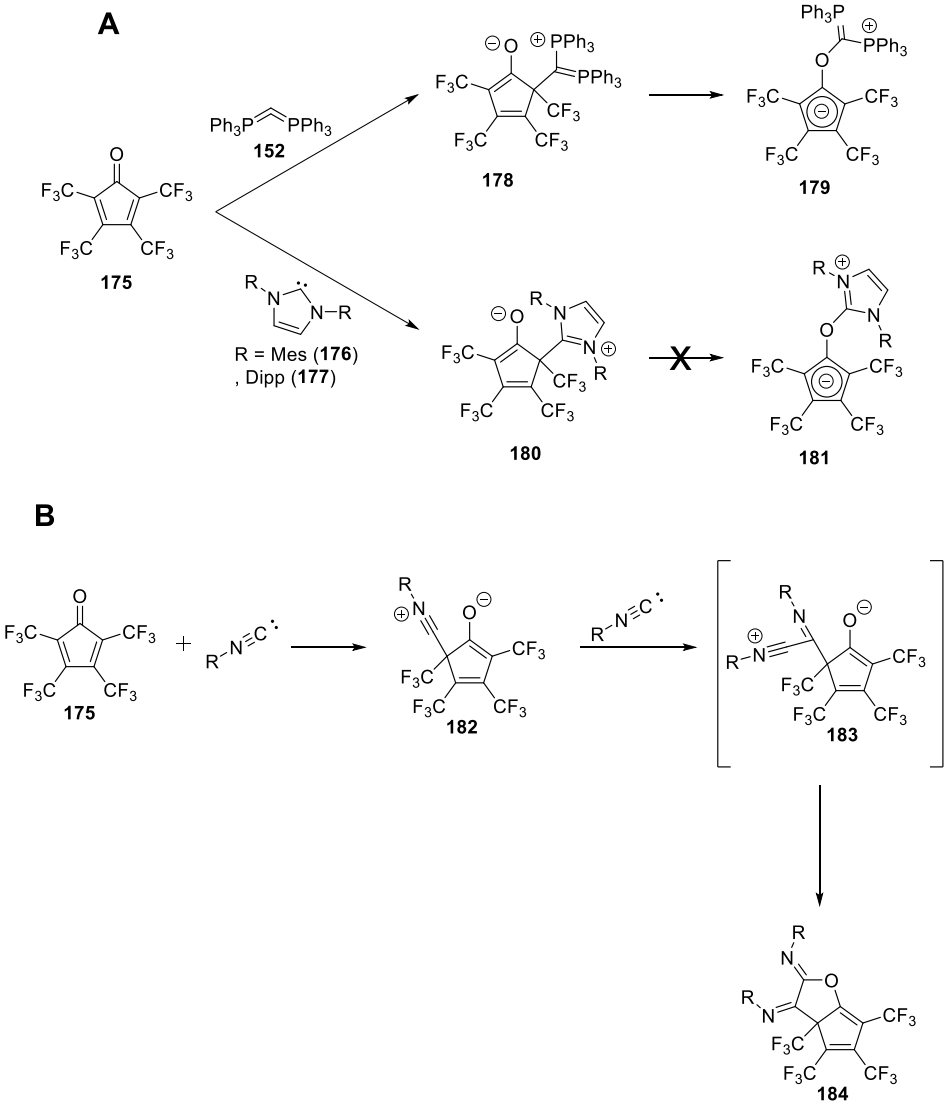
CDP was also reported to react with specific acyclic ketones to give cyclized[145] and/or acyclic compounds (Scheme 28).[146] Initial conjugate addition to the α,β-unsaturated ketone, followed by cyclisation and extrusion of triphenylphosphine oxide, resulted in the generation of a strained spirobicyclic cyclobutene species **170b**-**173b**.

Scheme 28: Wittig-type reactivity of a carbodiphosphorane towards acyclic ketones.



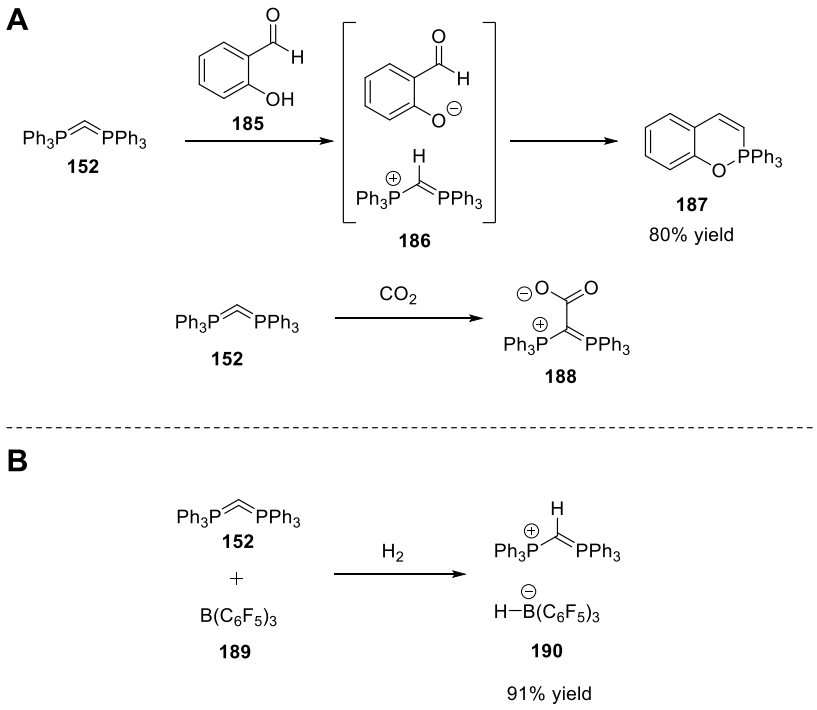
Noteworthy in this "reactivity" context are the distinct properties of NHCs and CDPs (Scheme 29). While both carbon nucleophiles undergo an identical initial vinylogous conjugate addition to tetrakis(trifluoromethyl)cyclopentadienone. Unlike carbenes CDPs and alkyl phosphines undergo a thermodynamic rearrangement while isonitriles undergo a second addition forming iminosubstituted dihydrofuran rings **184**.[147]

Scheme 29: Reactivity of a CDP vs. reactivity of an NHC and isocyanide (B).



In addition, CDP's reactivity with alcohols,[148,149] hydroxylamines,[150] and small molecules such as CO_2[151,152] has been investigated (Scheme 30). In the same line, CDPs have been part of frustrated Lewis pairs (FLPs) to activate molecular hydrogen, terminal alkynes, boranes, and silanes.[153,154]

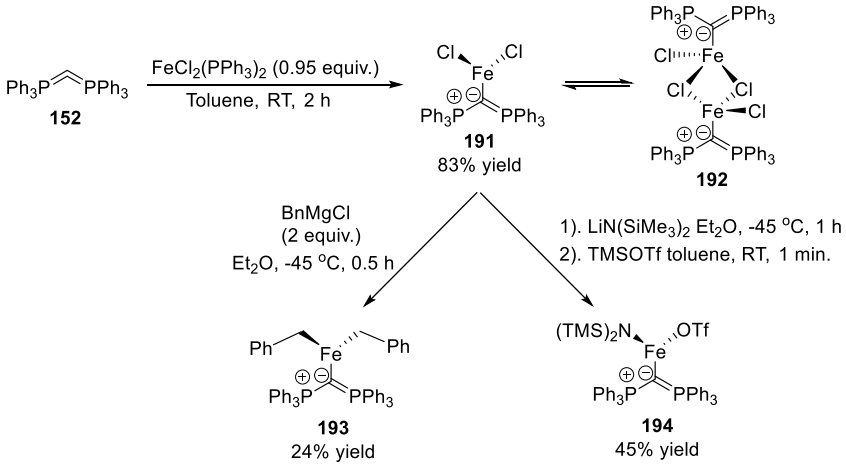
Scheme 30: Reactivity CDP with small molecules (A) and in frustrated Lewis pairs (B).



2.4 Stoichiometric CDP–Metal complexes

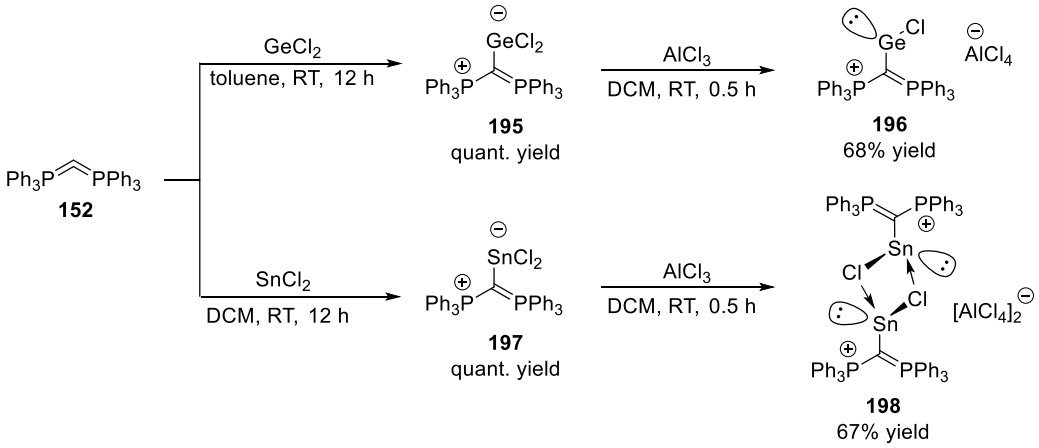
Various CDP–metal complexes were synthesised in a variety of contexts. Fürstner *et al.*[110] and Gandon *et al.*[155] reported various gold and gallium complexes with several distinct carbon(0) species. In a similar context, Stephan *et al.* synthesised iron complexes that displayed the CDP's ability to stabilise a rare three-coordinate iron geometry (Scheme 31).[138] These complexes were further exploited as synthons for low-oxidation state compounds. Complex **191** when reacted with two equivilents of benzyl Grignard formed the highly air-sensitive complex **193**. Displacement of one chloride from complex **191** using LiHMDS formed a complex uncharacterizable by X-ray diffraction. Dechlorination with TMSOTf afforded **194** of which X-ray quality crystals could be grown for characterisation. Attempts to form a two coordinate iron species from **191**, **193**, **194** have been unsuccessful.

Scheme 31: Formation of CDP–Fe complexes.[139]



The CDP's ability to stabilise reactive metal centres was further demonstrated through reaction with $GeCl_2$ (Scheme 32).[156] Abstraction of a chloride from the mono germyanyl complex forms a highly reactive $[GeCl]^+$ species stabilised by CDP. On extension of the protocol to tin rather than an expected $[SnCl]^+$ a dimeric form was isolated.

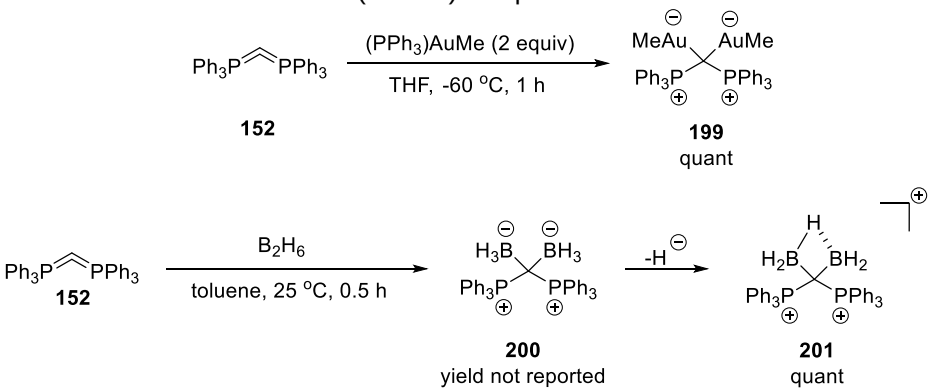
Scheme 32: Stabilisation of Ge(II) and Sn(II) species by a CDP.



Several other CDP–metal complexes have been synthesised under similar reaction conditions. For instance, complexes of a 1:1 stoichiometry between the CDP ligand and the corresponding metal salt have been reported for several transition metal salts, including copper,[157] silver and gold,[158,159] zinc and cadmium,[160] aluminum and indium,[161] manganese[162] as well as beryllium.[163] It is noted that the reaction of 0.5 equiv of CDP with the corresponding metal salt (Cu, Au, Ag) triggered the formation of various 2:1 complexes.[164] Additionaly CDP/carbonyl complexes were formed with tungsten[165] and rhenium.[166]

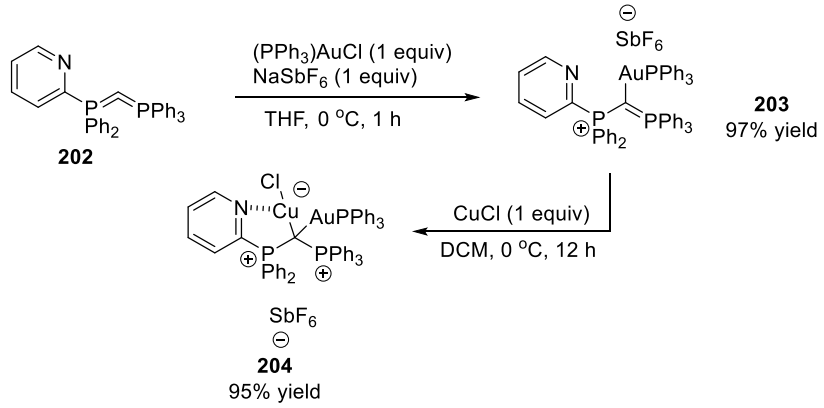
Although CDPs bear two lone pairs of electrons at the central carbon atom their full accessibility was initially doubtful. However, in 1976 Schmidbaur *et al.* reported the coordination of the CDP's central carbon atom to two gold centers, thus representing the first proof of the full availability of all four electrons at carbon (Scheme 33; top).[167] In 2009, the first complexation of *both* lone pairs to a main group element was uncovered (Scheme 33; bottom);[168] diborane was reacted with CDP to generate the corresponding double adduct that appeared to be hydride-bridged in dimethoxyethane (DME).

Scheme 33: Formation of diaurated and bis(borane) complexes of a CDP.



Such double (homo)complexations of a CDP was extended to a double (hetero)complexation using a non-symmetric pyridyl-tethered CDP (Scheme 34). Initially, after anion metathesis between $AuCl(PPh_3)$ and $NaSbF_6$, the CDP was complexed by Au(I). Subsequently, copper(I) chloride was shown to be complexed by the second lone pair of electrons at carbon; such complexation may be facilitated by an *ortho*-pyridyl's N–Cu interaction. While no characteristic application was reported for this heterobimetallic complex, it may open the possibility of carrying out dual catalysis by exploiting both metals.[168]

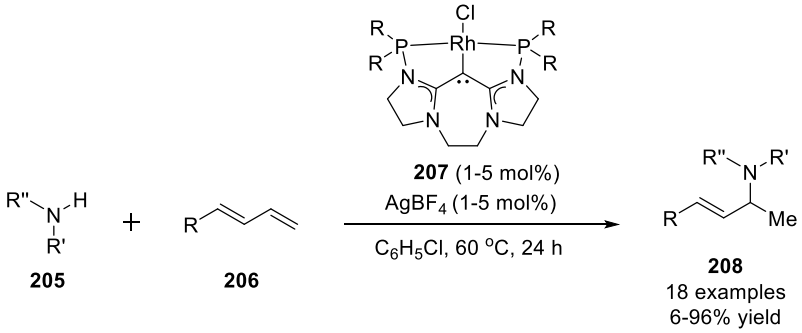
Scheme 34: Formation of a heterobimetallic complex of a CDP.



2.5 Catalytic Use of a Carbon(0) Species in Organic Synthesis

To the best of our knowledge, the use of carbon(0) compounds as catalysts has been limited to two sporadic examples. The first one was a catalytic hydroamination of terminal dienes facilitated by a Rh–CDC complex (Scheme 35).[169,170] Here, a good functional group tolerance was obtained at low catalyst loadings, with primary and secondary amines as well as a broad variety of dienes among successful substrates.

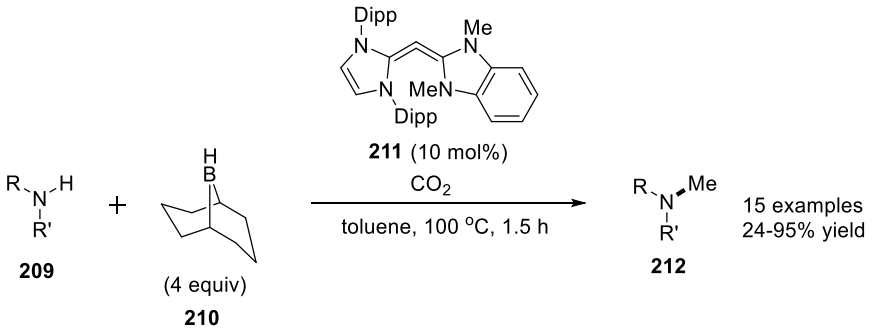
Scheme 35: Rh–CDP-catalysed hydroamination of dienes.



Unlike carbenes where a diverse range of electronic properties can be tuned a more limited range of carbon (0) compounds are available.[171] This may explain the underutilisation of carbon (0) compounds in catalysis. Pd–CDC complexes have been used to catalyse both Heck and Suzuki–Miyaura cross-coupling reactions.[172,173]

The first use of a carbon(0) species in organocatalysis was reported by Ong et al. for the N-methylation of aliphatic and aromatic primary as well as secondary amines using CO_2 (1 atm) and a borane as reagents (Scheme 36).[174]

Scheme 36: CDC-catalysed *N*–methylation of amines with carbon dioxide and a borane.[174]

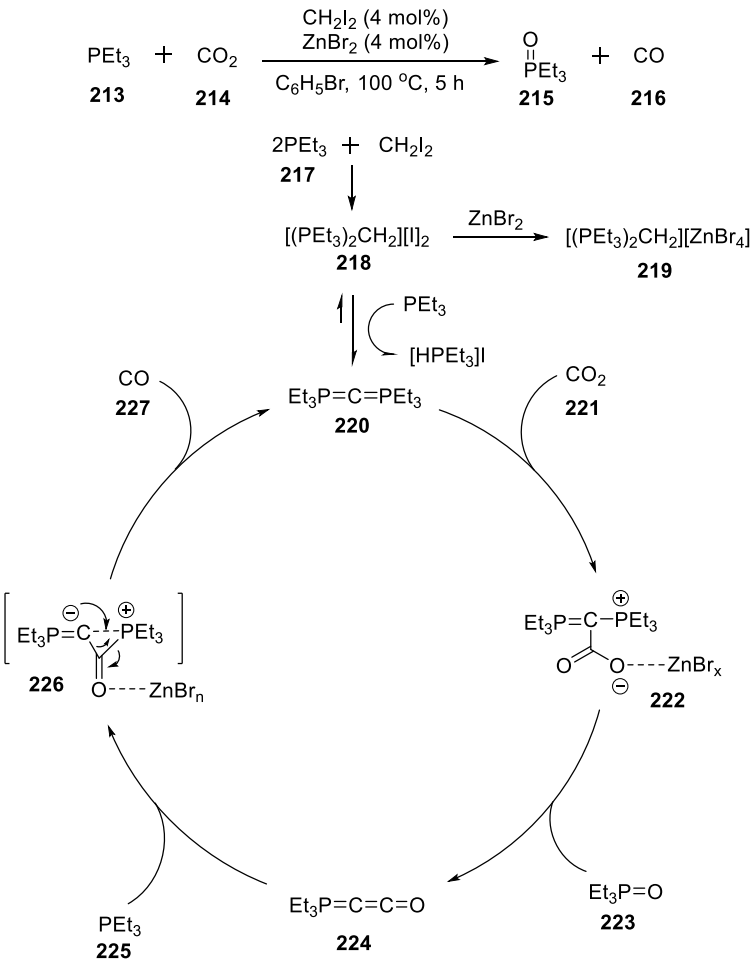


While the reductive amination by Ong demonstrated the CDC's potential for use in catalysis, CDPs have not been reported as organocatalysts to date. CDP's have been proposed as intermidiates in the reduction of CO_2.

It was observed that triethyl phosphine under an atmosphere of CO_2 led to a very slow formation of CO (overall reduction). The addition of a catalytic amount of a Lewis acid, $ZnBr_2$, and diiodomethane resulted in a substantial rate acceleration (Scheme 37).[175] Mechanistic investigations led to the isolation of the salt $[(Et_3P)_2CH_2][ZnBr_4]$ **220** starting from a mixture of CH_2I_2, triethyl phosphine and zinc bromide.

It was believed that the I_2 complex could be deprotonated by additional phosphine forming a CDP **220** *in situ*. This could then react with CO_2 as has been reported with other CDPs forming adduct **222**[175]. Thermolysis of this adduct generates the phosphaketene **224** which was believed to reform the CDP with extrusion of CO. While this postulation seems reasonable the ^{31}P NMR shift of +28.0 ppm seems unlikely when compared to other CDPs. This value is quite close to the values reported for the TMS adduct with CDP (vide supra) suggesting a possible CDP adduct rather than an actual CDP. While the formation of the ketene is shown conclusively through x-ray crystallography the NMR signals ascribed to a proposed CDP intermediate seem unlikely. Attempts to prepare a pure sample of the carbodiphosphorane for use in catalysis were unsuccessful.

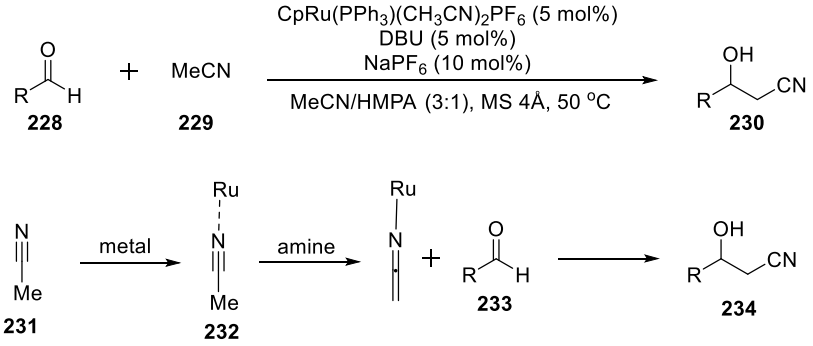
Scheme 37: Catalytic reduction of CO_2 *via* a supposed *in situ*-generated CDP species.[175]



2.6 Catalytic Activation of Alkyl Nitriles

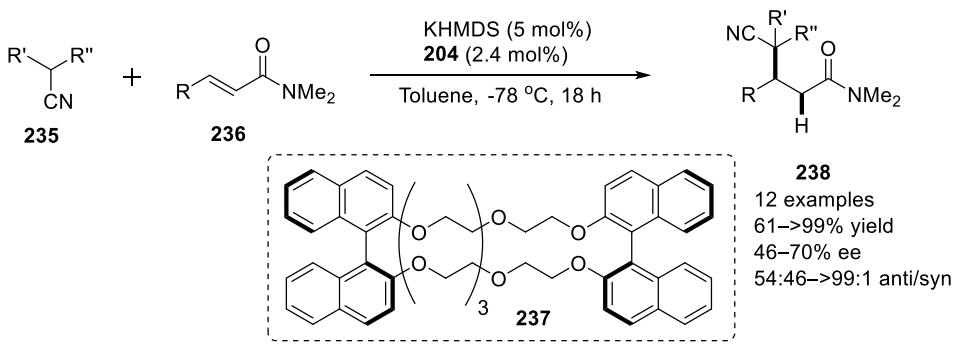
Shibasaki *et al*. reported the cooperative catalytic activation of acetonitrile by a ruthenium complex and DBU for the subsequent nucleophilic addition to aldehydes (Scheme 38).[176] Under the mild conditions ester functionalities remained intact and enolisable aldehydes were tolerated. In addition, imines proved to be successful electrophiles.

Scheme 38: Ru-catalysed activation of acetonitrile for aldol-type additions.[176]



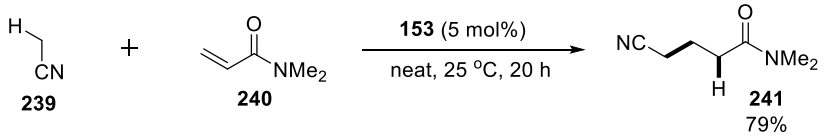
After this seminal work, additional research into the nucleophilic addition to aldehydes has been carried out using various metal complexes.[177-184] Additionally, isatins,[185] imines,[186,187] and esters[188] have been used as electrophiles. These approaches rely on lowering the pK_a value of acetonitrile through Lewis acid activation. In a similar context, Brønsted base catalysis was reported for the activation of alkyl nitriles in view of an asymmetric conjugate addition to Michael amides (Scheme 38).[189] Here, K–HMDS was combined with an enantiomerically enriched crown ether **237** to generate an effective chiral catalyst system. While several substituted alkyl nitriles displayed good reactivity, the substrate scope regarding heteroaromatics and α-substituted α,β-unsaturated amides **236** was found to be poor. Importantly, the simplest alkyl nitrile, acetonitrile, was not tolerated under the mild reaction conditions forming a complex mixture. Such drawbacks may be related to the presence of the metal cation, which may trigger a polymerisation of the Michael acceptor rather than a C–C bond formation between the two substrates. In turn, while metal catalysis may be not suitable for the use of acetonitrile, metal-free organocatalysis may be an option to overcome such an issue.

Scheme 39: Congugate addition of alkyl nitriles to α,β-unsaturated amides.



In order to test this hypothesis, *N*,*N*-dimethylacrylamide was reacted in acetonitrile at ambient temperature overnight using 5 mol% loading of CDP (Scheme 40). Gratifyingly, the corresponding conjugate adduct **242** was formed in 79% yield; a potential 1,2-addition was not observed.

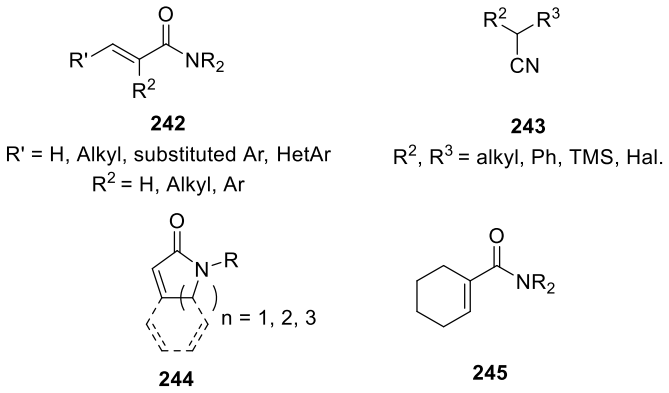
Scheme 40: Earlier experiment in our group –towards CDP catalysis– performed by Hanno Kossen.



2.7 Aims

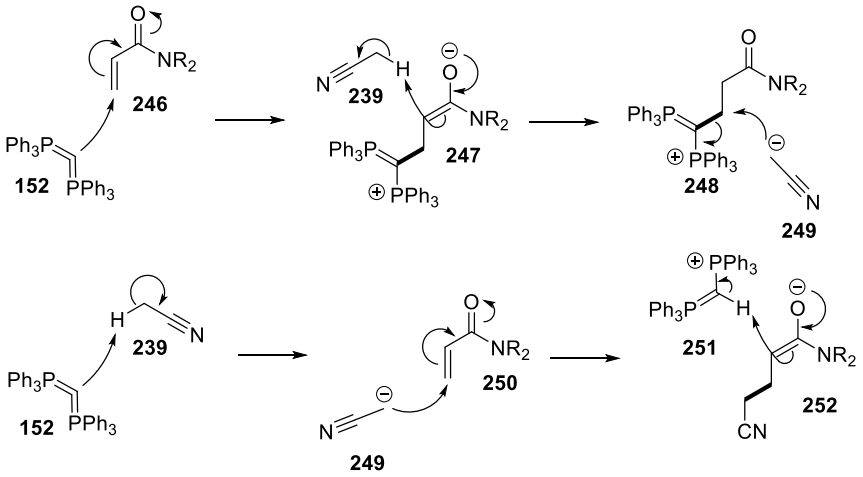
Based on the preliminary work carried out by Hanno Kossen, the goal of this project was to truly develop an unprecedented CDP catalysis, and to show the significance with respect to other organocatalysts as well as metal-centred catalysts. Also, in Kobayashi's study the substrate scope proved to be limited. In turn, the development of a general procedure applicable to a wide range of alkyl nitriles was another worthwhile goal; additional substrates were proposed to test the robustness of the intended transformation (Scheme 41).

Scheme 41: Proposed substrates for the catalytic alkylcyanation of Michael acceptors.



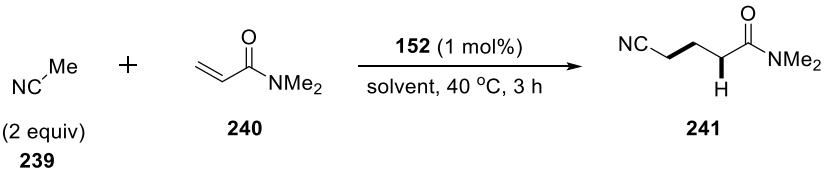
Furthermore, the examination of the potential mechanisms of such unprecedented catalytic use of a CDP was an important aim; two plausible pathways could be imagined (Scheme 42). The postulated Lewis base pathway would involve conjugate addition to the Michael acceptor followed by deprotonation of acetonitrile by the *in situ*-generated amide-enolate (top). Alternatively, a Brønsted base pathway would be conceivable through direct deprotonation of acetonitrile followed by the conjugate addition of the resulting carbanion to the Michael acceptor.

Scheme 42: Proposed Lewis base and Brønsted base mechanisms.



2.8 Solvent screen

Table 14: Solvent screen for the 1, 4 addition reaction.



entry	***solvent***	dielectric constant (ε)	yield (%)	mass balance (%)
1	DMF	38.2	NR[a]	97
2	Neat	37.5	Quant.	101
3	NMP	32	NR[a]	70
4	PhCN	26	NR[a]	98
5	TCE	10.4	NR[a]	93
6	THF	7.5	NR[a]	94
7	TBME	2.6	NR[a]	96
8	toluene	2.4	NR[a]	97
9	dioxane	2.3	NR[a]	99
10	^{t}BuCN	-	NR[a]	98

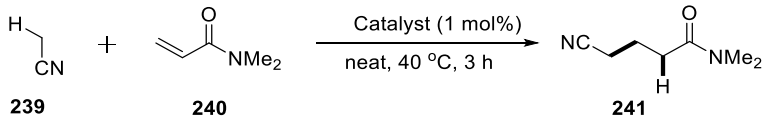
[a] No reaction only starting material recovered.

While the use of acetonitrile neat worked very effectively it would be desirable for other expensive nitriles if other solvents could be used. Various polarity solvents were investigated though no reaction was observed in all cases; despite good solubility. Generally good mass balances were observed except for the cyclic lactam NMP. The lack of reactivity in solvents such as TCE was unsurprising; and visible decomposition and decolouration of the solution was observed. Other nitrile solvents such as benzonitrile and trimethylacetonitrile also failed.

2.9 Control Experiments

In order to stress the significance of the observed catalytic use of CDP, other base catalysts were examined. Kobayashi reported an undesirable reactivity by using KHMDS in the presence of a crown ether ligand; such issue may be triggered by the presence of a metal cation. Thus, other potential metal–amide catalysts were screened at 1 mol% loading (Table 15). Here again, very poor reactivity and mass balance were observed with a variety of metal–amide species. On the other hand, the catalytic use of CDP provided the intended conjugate addition product in 99% yield.

Table 15: Control experiments with potential metal–amide catalysts (vs. CDP).[a]



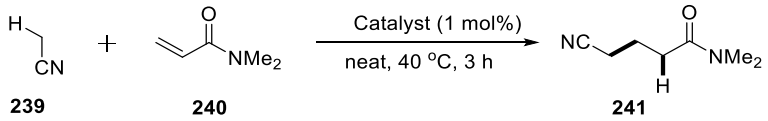
239 **240** **241**

entry	***Catalyst***	yield (%)[b]	mass balance
1	LTMP	14%	14%
2	LDA	NR[b]	85%
3	LHMDS	NR[b]	2%
4	NaHMDS	23%	23%
5	$Zn(HMDS)_2$	NR[b]	77%
6	$Sn(HMDS)_2$	1%	71%
7	$Gd(HMDS)_3$	NR[b]	85%
8	$Yb(HMDS)_3$	NR[b]	88%
9	CDP	99%	99%

[a] Reactions were carried out in duplicate and an average reported. The yield and mass balance were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene. [b] No reaction only starting material recovered.

Next, a variety of metal–alkoxides were screened because such compounds were shown to catalyse the deprotonation of pro-nucleophiles with challenging pK_a values.[99,100,190] Also, the propensity of these compounds to form stabilised radicals[191,192] that may possibly abstract the α-hydrogen of an alkyl nitrile, cannot be neglected. Similar to the results with amides, a variety of metal–alkoxides gave essentially no reactivity with mostly a poor mass balance (Table 16).

Table 16: Control experiments with potential metal–alkoxide catalysts (vs. CDP).[a]



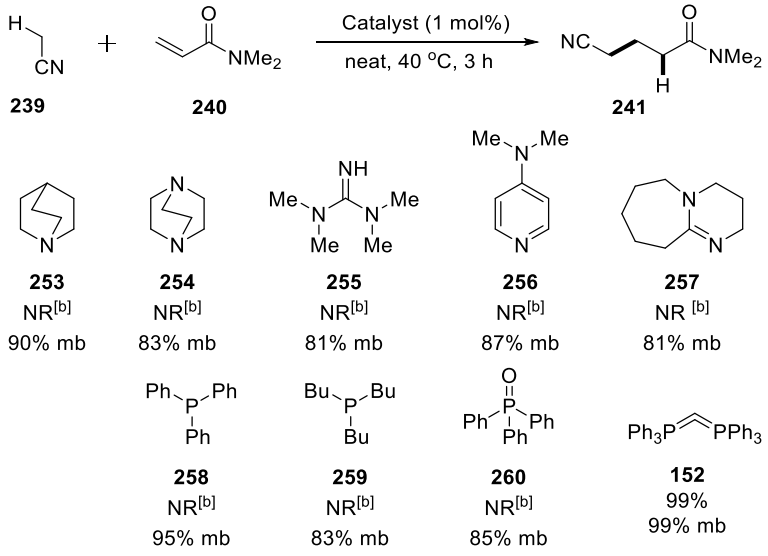
239 **240** **241**

entry	***Catalyst***	yield (%)[a]	mass balance
1	LiO^{t}Bu	NR[b]	0%
2	NaO^{t}Bu	NR[b]	43%
3	KO^{t}Bu	NR[b]	0%
4	$Mg(OEt)_2$	NR[b]	84%
5	$Ca(OMe)_2$	NR[b]	60%
6	$Sr(O^iPr)_2$	NR[b]	83%
7	$Ba(O^iPr)_2$	NR[b]	83%
8	$Fe(OEt)_3$	NR[b]	100%
9	$Zn(O^tBu)_2$	NR[b]	89%
10	$In(O^iPr)_3$	NR[b]	81%
11	CDP	99%	99%

[a] The yield and mass balance were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene. Reactions were carried out in duplicate and an average reported. [b] No reaction only starting material recovered.

These results confirmed to some extent Kobayashi's observation and our hypothesis regarding the issue with metal traces in such sensitive acrylamide substrates. While the goal to report an unprecedented CDP catalysis was paramount, the significance would be diminished if the reaction could be accomplished using more commonly used organobases. In turn, a variety of common organobases[193-195] were screened (Scheme 43). Gratifyingly, the reaction with amines, guanidines, amidines and phosphines gave no reaction under the mild conditions.

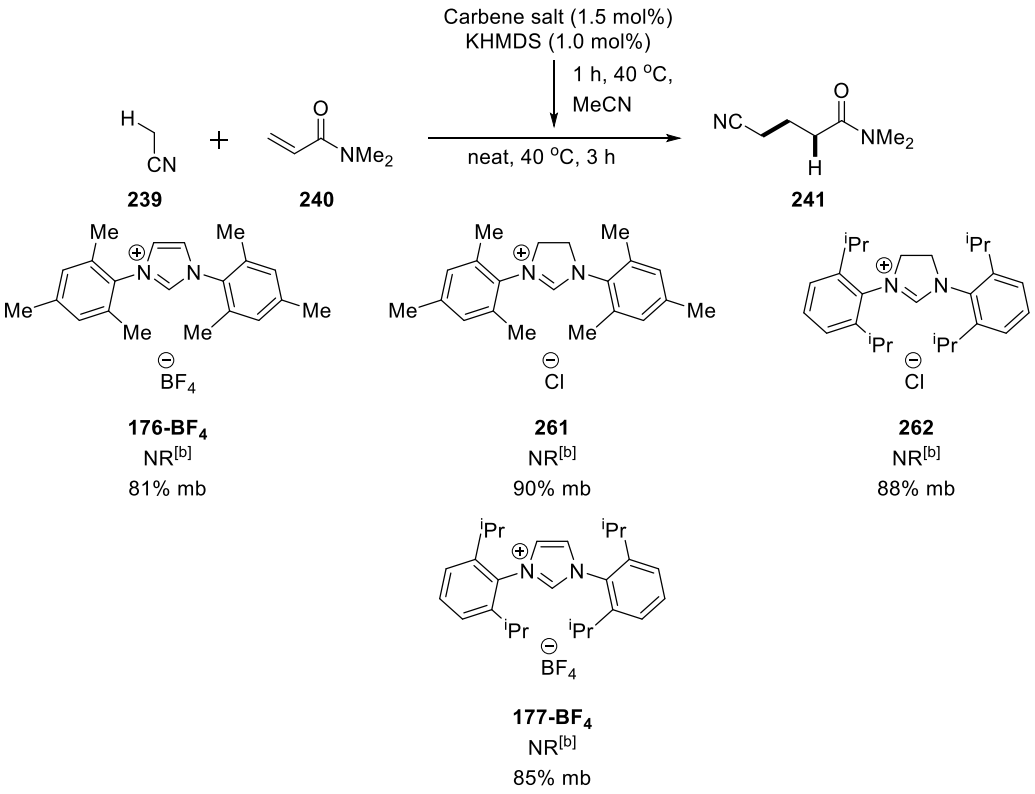
Scheme 43: Control experiments with commonly used Lewis base catalysts (vs. CDP).[a]



[a] Reactions were carried out in duplicate and an average reported. The yield and mass balance were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene. [b] No reaction only starting material recovered.

In addition, various *N*-heterocyclic carbenes bearing *N*-aryl groups were found to not give any reactivity in the model transformation (Scheme 44); here the mass balances proved to be very good. These data may highlight the fact that carbones are more basic and/or nucleophilic than carbenes.

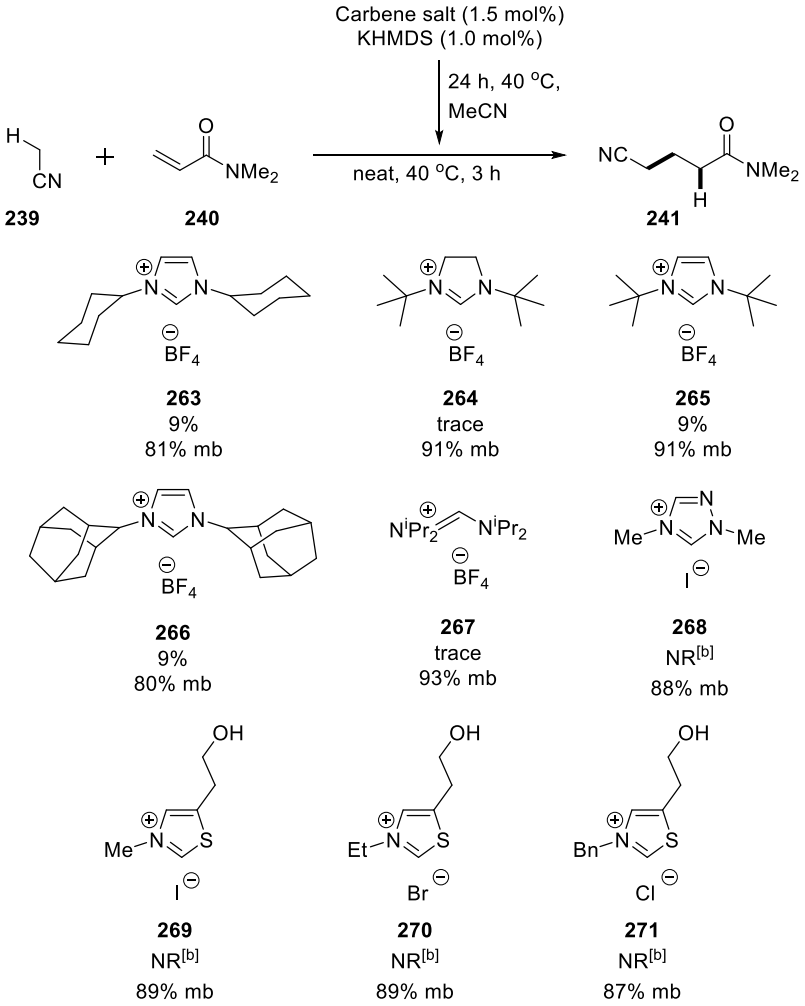
Scheme 44: Control experiments with "aromatic" *N*-heterocyclic carbenes (vs. CDP).[a]



[a] Reactions were carried out in duplicate and an average reported. The yield and mass balance were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene. [b] No reaction only starting material recovered.

In the same line, "aliphatic" NHCs were examined in order to further compare carbenes with the CDP (Scheme 45). While a reaction was not observed at all with triazolium- and thiazolium-based NHCs as well as an acyclic (alkyl)amino carbene, a very modest reactivity was observed with a few ordinary *N*-alkyl carbenes. In order to ensure that the deprotonation of the corresponding precursor salts was successful, an identical pre-stirred solution of the *in situ*-formed carbene **177** was reacted with BEt_3 and analysed by ^{11}B NMR spectroscopy (generation of a boron–ate complex). A shift in ^{11}B NMR from 80 ppm to ~0 ppm occurred reproducibly.

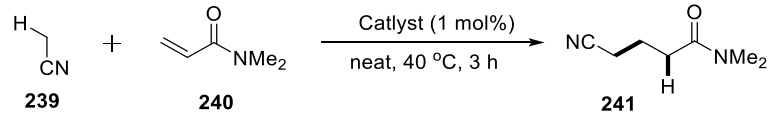
Scheme 45: Control experiments with "aliphatic" *N*-heterocyclic carbenes (vs. CDP).[a]



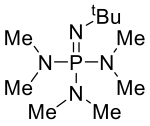
[a] The yield and mass balance were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene. Reactions were carried out in duplicate and an average reported.
[b] No reaction only starting material recovered.

A vast amount of research has been published regarding the use of metal-centred superbases in organic synthesis.[196] Typically, these bases may represent a combination of an alkyl lithium species and a metal alkoxide through exchange,[197-201] e.g. the Schlosser-type LICKOR bases. More recently however, metal-free organic superbases have been synthesised and made commercially available. Phosphazene or Schwesinger[202-204] and Verkade[205-207] bases are *N*- and *P*-centred strong bases, respectively. These species do have extremely high pK_a values as demonstrated in Scheme 46. Most of the superbases examined were as proficient at enabling the model transformation as CDP. However, compared to the earlier base screenings, the observed reactivity was generally higher. As for phosphazene bases, increasing the basicity up to P4-^{t}Bu resulted in an increased reactivity going from P1 to P2 to P4. Similarly, Verkade's "^{i}Pr" base was also a successful catalyst while lower reactivity was observed for its derivatives. While some of these bases gave modest to good reactivity, none were as competent as CDP. These data validated our initial goal of using a CDP in an organocatalytic context in order to surpass the reactivity observed with metal–base species.

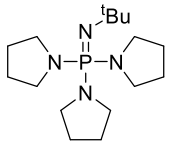
Scheme 46: Control experiments with metal-free organic superbases (vs. CDP).[a]



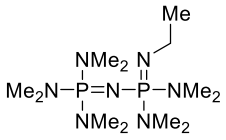
239 **240** **241**



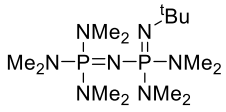
272
pK_{BH+} 26.9 (MeCN)
4%
88% mb



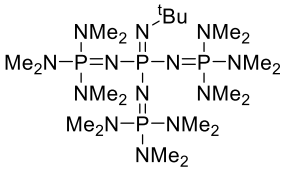
273
pK_{BH+} 28.4 (MeCN)
NR[b]
90% mb



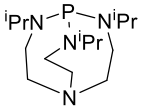
274
pK_{BH+} 32.9 (MeCN)
14%
90% mb



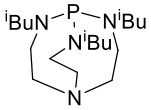
275
pK_{BH+} 33.5 (MeCN)
34%
84% mb



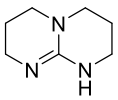
276
pK_{BH+} 41.9 (MeCN)
85%
85% mb



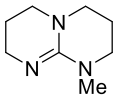
277
pK_{BH+} unreported (MeCN)
83%
88% mb



278
pK_{BH+} 33.6 (MeCN)
23%
86% mb



279
pK_{BH+} 26.0 (MeCN)
trace
89% mb

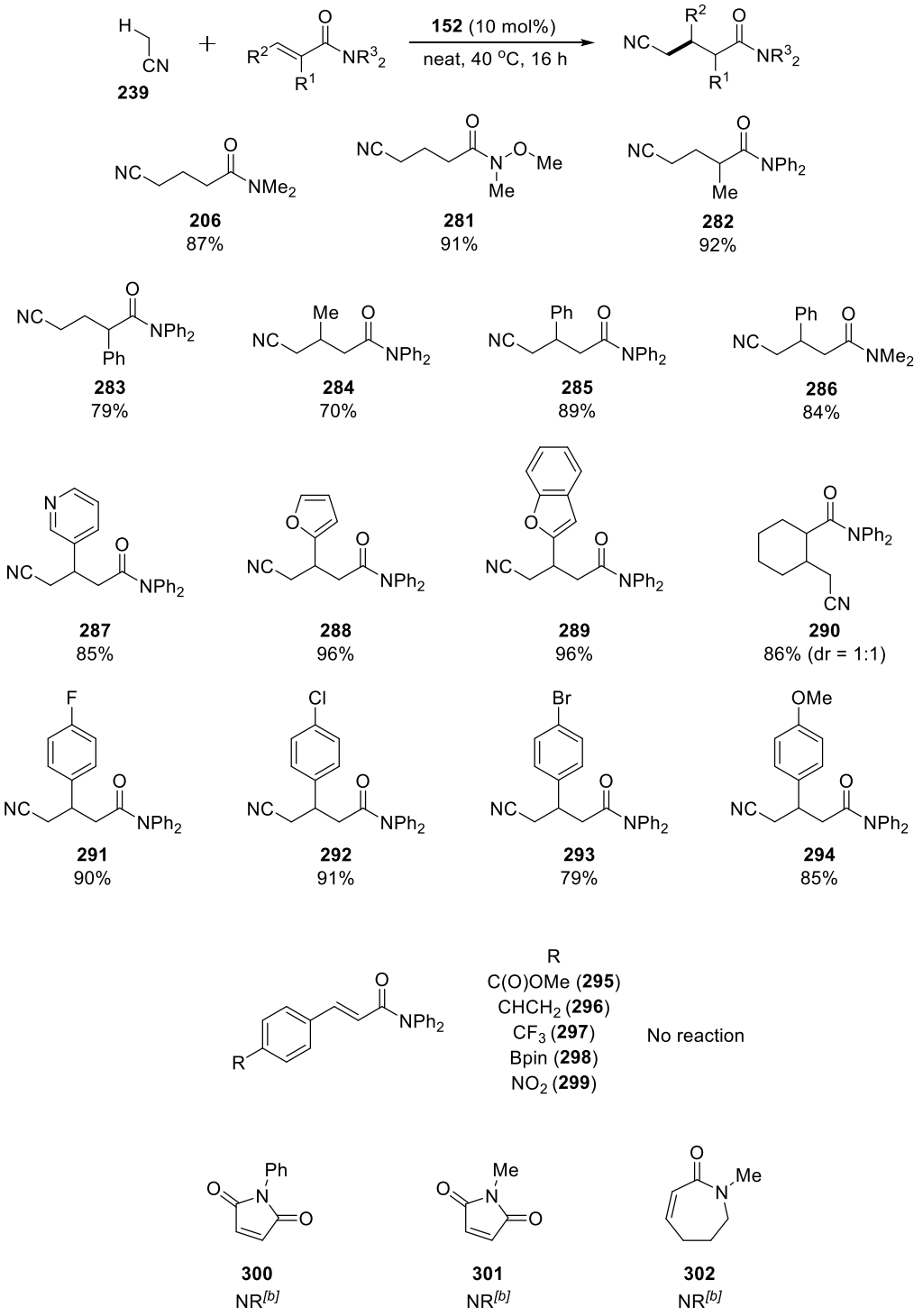


280
pK_{BH+} 25.5 (MeCN)
NR[b]
83% mb

[a] The yield and mass balance were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene. Reactions were carried out in duplicate and an average reported. [b] No reaction only starting material recovered.

A wide range of α,β-unsaturated amides were prepared to investigate the applicability and tolerance of the catalytic conjugate addition using acetonitrile. In addition to the commercially available *N*,*N*-dimethyl acrylamide, the corresponding Weinreb amide was synthesized; among others (see SI). Next, the scope for the catalytic use of CDP was examined regarding the various α,β-unsaturated amides (Scheme 47). α-Substitution was tolerated with both methyl and phenyl groups giving good NMR yields. The use of the β-substituted crotyl amide as well as β-substituted heteroaromatic amides required heating to 80 °C, while the β-substituted cinnamyl amide reacted at 40 °C. For the α,β-disubstituted cyclohexene-derived amide a mixture of diasteroisomers was obtained. Cyclic Michael systems such as the maleimides and unsaturated lactames failed to react, even under more pushing conditions.

Scheme 47: Scope for the catalytic conjugate addition of acetonitrile to α,β-unsaturated amides.

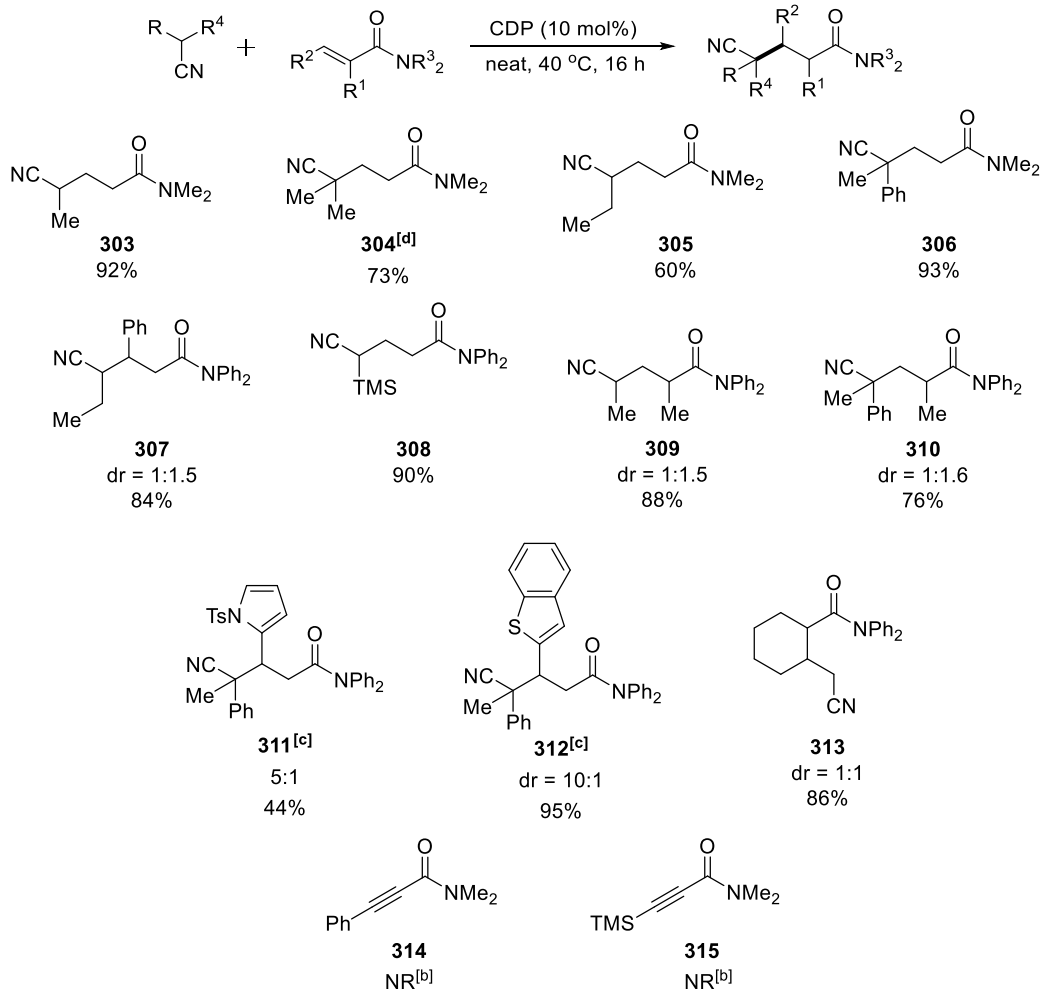


[a] Reactions were carried out according to *General Procedure V*. [b] NR = no reaction: a reaction was not observed; only starting materials recovered. [c] Reaction temperature: 80 °C.

In addition to acetonitrile, other aliphatic nitriles were examined in this catalytic conjugate addition (Scheme 48). Gratifyingly, these pro-nucleophies were all activated using a catalytic amount of CDP. In addition, trimethylsilyl acetonitrile as well as α-methylbenzyl cyanide reacted well; both substrates contain a group ($SiMe_3$ or Ph) that allows the stabilisation of the adjacent negative charge formed.

While it was hoped that chlorinated and brominated acetonitrile would be tolerated under the standard conditions with *N*,*N*-dimethyl acrylamide, a productive reaction was not observed by ^{1}H NMR spectroscopic analysis of a reaction aliquot; in principle, such failure could be ascribed to the ability of the CDP to dehalogenate the nitrile, however, such by-product was not detectable (^{31}P NMR spectroscopy). The reaction using mono-fluorinated acetonitrile was possible for a few selected substrates, but as it was formed with low diastereoselectivity it was not isolated. The use of methoxy- and phenoxy-substituted acetonitrile failed to give any reaction product despite forcing conditions to 80 °C. Where substituted amides were used the formation of diastereoisomers generally occurred with low selectivity. However, the use of several substrates allowed a certain level of diastereocontrol. For instance, the use of the β-benzothiophene-substituted Michael amide, the diastereoselectivity of 5:1 (at 40 °C) could be improved to 10:1 (30 °C); further experiments to achieve higher level of disstereoselection are on-going. Finally, it is noted that alkyne-derived Michael amides failed to give any reactivity with any of the nitriles investigated.

Scheme 48: Scope for the catalytic conjugate addition of alkyl nitriles to α,β-unsaturated amides.[a]

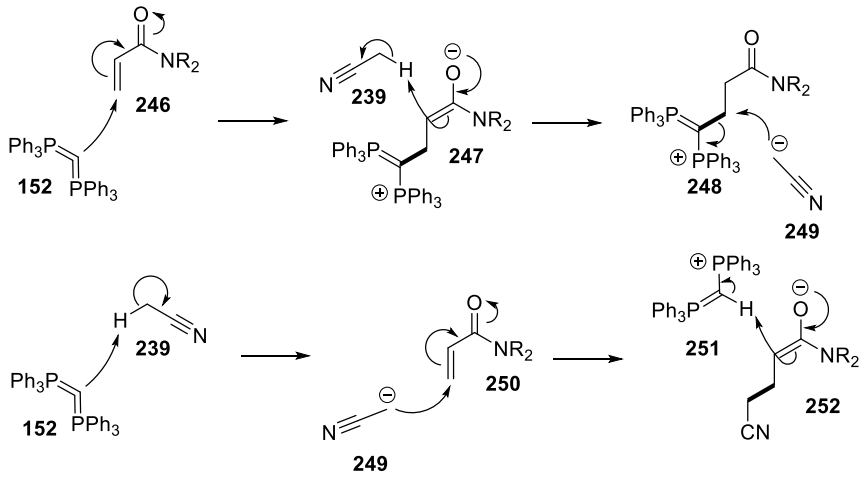


[a] The yield and mass balance were determined by ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture after addition of an internal standard DBE (0.25 M) in mesitylene. [b] No reaction only starting material recovered. [c] Reactions were carried out at 30 °C. [d] Reactions were carried out at 80 °C.

2.10 Possible Activation Pathways by CDP

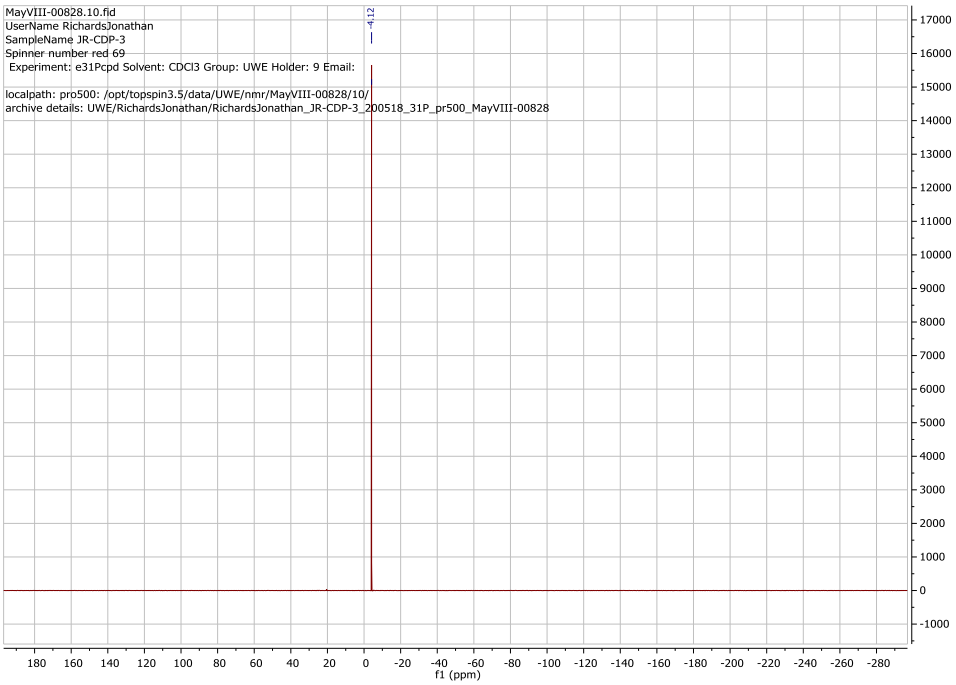
Being both a powerful Lewis base and Brønsted base, CDP may catalyse the reaction in two different ways. First, the CDP –as a Lewis base (nucleophile)– may add in a conjugate fashion to the Michael acceptor forming a zwitterionic amide-derived enolate, which should be apt to deprotonate acetonitrile. Thereby, the acetonitrile-anion (nucleophile) and the phosphonium-substituted amide (electrophile) would be formed. A simple nucleophilic substitution would (re)generate both product and CDP catalyst (C–C bond formation). Second, the CDP –as a Brønsted base– may directly deprotonate acetonitrile to form the acetonitrile-anion (nucleophile). The latter woud undergo conjugate addition to the Michael acceptor (electrophile; C–C bond formation). Here, the generated amide-derived enolate may be protonated by CDP–H^+ (catalysis) or the next molecule of acetonitrile (initiation), so to provide turnover of the reaction. While determining the exact reaction pathway may be challenging, a partial investigation seemed possible through ^{31}P NMR spectroscopy.

Scheme 39: Potential pathways for the catalytic use of CDP: Lewis base vs. Brønsted base activation.



^1H NMR decoupled spectroscopy of the CDP starting material displayed a sharp singlet at –4.1 ppm. In order to investigate the formation of reaction intermediates (by nucleophilic addition or deprotonation) variable-temperature experiments were carried out using dimethylacrylamide and various alkyl nitriles. Reacting the CDP with MeCN (1 equiv) in benzene-d_6 led to the formation of a small signal at +20.4 ppm. This signal displays a similar in chemical shift to the product of the “addition of water” to CDP, thus suggesting a protonated CDP species. Variation of the temperature had very little influence on the intensity of the observed signal.

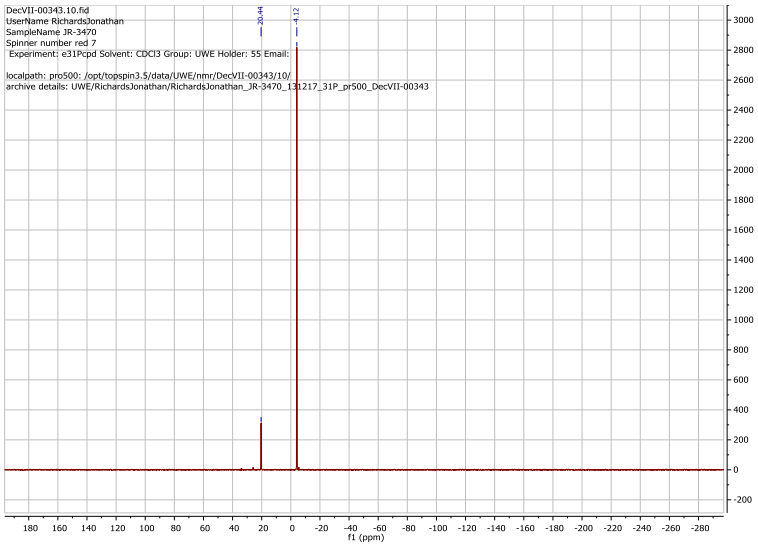
Chart 3: ^{31}P NMR spectroscopic analysis of CDP.



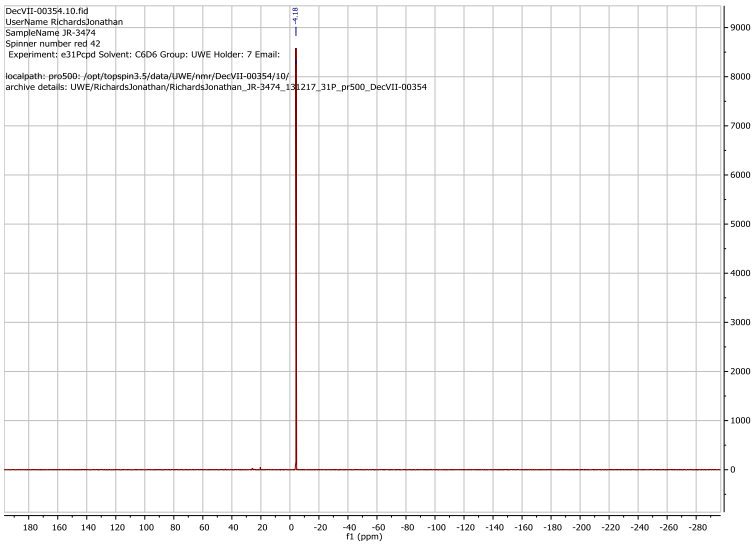
The use of other aliphatic nitriles, namely propionitrile and isobutyronitrile gave lower and significantly lower concentrations of the +20.4 peak, respectively. When the CDP and dimethylacrylamide were combined, the use of variable-temperature ^{1}H and ^{31}P NMR spectroscopy showed only a signal at –4.1 ppm, which was not influenced by the temperature. This result may suggest that the CDP first deprotonates the acetonitrile rather than adding as a nucleophile to the Michael amide. However, further experiments are required to fully elucidate the mode of action.

Chart 4: ^{31}P NMR spectroscopic analysis of CDP with each reagent: (a) acetonitrile, (b) *N*,*N*-dimethyl acryl amide.

(a)



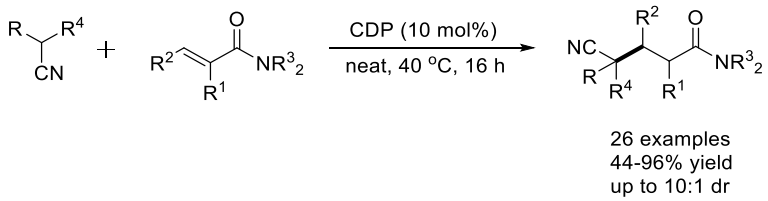
(b)


DecVII-00354.10.fid
UserName RichardsJonathan
SampleName JR-3474
Spinner number red 42
Experiment; e31Pcpd Solvent: C6D6 Group: UWE Holder: 7 Email:
localpath: pro500: /opt/topspin3.5/data/UWE/nmr/DecVII-00354/10/
archive details: UWE/RichardsJonathan/RichardsJonathan_JR-3474_131217_31P_pr500_DecVII-00354
4.18
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
180 160 140 120 100 80 60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200 -220 -240 -260 -280
f1 (ppm)

2.11 Conclusions and Future Work

The first catalytic use of a CDP was developed in organic synthesis, in the context of catalytic conjugate additions of aliphatic nitriles to α,β-unsaturated amides (Scheme 48). The catalyst proved to be very active in neat nitriles, though poorly in other solvents. In the context of substrate scope and functional group tolerance, a reasonable range of substitution motifs and functionalities was developed, including a variety of heterocyclic fragments. In case of substituted Michael acceptors and/or aliphatic nitriles, low diastereoselectivites were observed in most cases although encouraging signs started to appear in a few specific cases (with *dr* ~ 10:1). The activation pathway for this catalytic use of CDP has been only investigated in a very preliminary form that does not allow any definite conclusion at this stage. However it would appear that initial deprotonation of the acetonitrile by the CDP followed by 1, 4 addition to the unsaturated amides is the most likely candidate. Whether the CDP acts catalytically or initiates the formation of the amide enolate is unknown.

Scheme 49: Catalytic use of CDP for the conjugate addition of alkyl nitriles to α,β-unsaturated amides.



Future work on this project could focus on the use of different phosphine fragments to be incorporated in the CDP core as such alteration may substantially influence the catalytic activity. Such modification may be of particular interest in view of asymmetric catalysis triggered by an enantiomerically enriched CDP; the latter may be accessible through incorporation of an enantiomerically enriched phosphine into the carbone core.

3.0 Experimental

3.1 General Experimental

Reaction Setup: All reactions were carried out under inert atmospheres using N_2 in a MBraun glovebox; otherwise reactions were carried out under dry Ar using balloons. Unless otherwise stated, chemicals were purchased from Sigma, Alfa, Acros or Fischer and used without further purification. Toluene, diethyl ether and THF were distilled over Na with benzophenone indicator and stored over 4 Å molecular sieves. All other solvents were dried and purified in a solvent purification system using Grubbs method[208] and stored over 4 Å molecular sieves. Sieves were activated at 300 ^{o}C for 72 h under high vacuum. Solvent dryness was confirmed using coulometric Carl-Fischer apparatus. Catalytic reactions were run at either 25, 30, 40, 60 or 80 ^{o}C in constant temperature sand baths with a stirring rate of 400 rpm. 7 cm screw seal vials were used as catalytic reaction vessels and were further sealed with Teflon and parafilm. All reactions were stirred magnetically. All glassware was stored for a minimum one hour in a hot (80 ^{o}C) oven and cooled under inert gas. For lower than ambient temperature standard cooling baths were used.

NMR spectroscopy: ^{1}H NMR spectra were recorded on Bruker AVA400 (400 MHz) with BBFO+ probe, Bruker AVA500 (500 MHz) with DCH cryo-probe, Bruker PRO500 (500 MHz) with Prodigy cryo-probe, or Bruker AVA600 (600 MHz) with TCI cryo-probe spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using TMS as an internal standard ($Si(CH_3)_4$, δ = 0.00 ppm). In the absence of TMS, residual solvent in deuterated solvents were used as an internal standard ($CDCl_3$, δ = 7.26 ppm or C_6D_6, δ = 7.16 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. ^{13}C NMR spectra were recorded on Bruker AVA500 (125 MHz), or Bruker AVA600 (150 MHz) spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane as an internal standard ($Si(CH_3)_4$, δ = 0.00 ppm). In the absence of TMS, residual deuterated solvent was used as an internal standard ($CDCl_3$, δ = 77.0 ppm or C_6D_6, δ = 128.4 ppm. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of lithium chloride without internal standard. ^{11}B NMR spectra were recorded on Bruker AVA400 (128 MHz) or Bruker PRO500 (160 MHz) spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of trifluoroborate diethyletherate without internal standard. ^{19}F NMR spectra were recorded on Bruker AVA400 (376 MHz) or Bruker PRO500 (470 MHz) spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of trichlorofluoromethane without internal standard. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of sodium chloride without internal standard. ^{31}P NMR spectra were recorded on Bruker AVA400 (162 MHz) or Bruker PRO500

(202 MHz) spectrometers. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of phosphoric acid without internal standard.

Mass Spectrometry: Mass Spectrometry was provided by the Edinburgh University School of chemistry and performed on either a Bruker ESI Micro-Tof or a ThermoElectron MAT 900 sector.

IR Spectroscopy: Infra-red spectra were recorded on a Shimadzu IRAffinity-1 instrument on isolated samples using the attenuated total reflectance sampling technique provided in the School of Chemistry, The University of Edinburgh.

Chromatography: Analytical thin-layer chromatography (TLC) was performed using Merck Silica gel 60 F_{254} plates. The plates were visualised using either UV light, anisaldehyde stain, $KMnO_4$ or iodine stain. Flash column chromatography was performed using Merck Geduran P60 43-60 μm silica gel using winchester grade solvents: Petroleum ether (VWR); diethyl ether (Aldrich); hexane (Aldrich); dichloromethane (Fischer)**;** and ethyl acetate (VWR). High performance liquid chromatography (HPLC) was performed on a Shimadzu LC-20AT with a SPD-20A detector on 4.6 x 250 mm columns from Diacel using winchester HPLC grade solvents which were degassed by ultrasonication. Preparative thin-layer Chromatography (PTLC) was carried out on self-prepared plates prepared from Wakogel B-5F (particle size 45 μm) from WAKO.

Melting points: Melting points were carried out using Gallenkamp melting point apparatus and are uncorrected.

Commercially available indoles: 4-Methyl indole: Fluorochem (>97%), 5-Methyl indole: Sigma Aldrich (99%), 6-Methyl indole Sigma Aldrich (97%), 4-Aza indole: Fluorochem (>97), 5-Azaindole: Alfa Aesar (98%), 6-Azaindole: Fluorochem (>97%), 7-Azaindole: Sigma Aldrich (98%), 3-Chloro-7-azaindole: Sigma Aldrich (97%), 4-Chloro-7-azaindole: Sigma Aldrich (97%), Tryptamine: Sigma Aldrich (98%), 5-Cyanoindole: Sigma Aldrich (99%), 4-Hydroxyindole: Alfa Aesar (98%), 5-Methoxyindole: Sigma Aldrich (99%), 5-Methoxy-6-azaindole: Sigma Aldrich (96%), 6-Fluoro-7-methylindole: Sigma Aldrich (97%), 5-Bromo-7-azaindole: Sigma Aldrich (96%), 5-Trifluoromethylindole: Sigma Aldrich (97%), 4-Cyano-7-azaindole: Fluorochem (>97%), 5-Aminoindole: Fluorochem (>97%).

Commercially available nitriles: Acetonitrile: Acros (>99%), Propionitrile: Acros (99%), Isobutyronitrile: Sigma Aldrich (99%), Butyronitrile: Acros (99%), α-methylbenzylcyanide: Alfa (98%), Trimethylacetonitrile: Sigma (98%), Fluoroactonitrile: Sigma Aldrich (98%), Chloroactonitrile: Fluka (99%), Bromoactonitrile: Sigma Aldrich (97%), Benzyl

cyanide: Sigma Aldrich (98%), Methoxyacetonitrile: Sigma Aldrich (>98%), Phenoxyacetonitile: Sigma Aldrich (98%).

3.2 General Procedures

Base screening of indole coupling (general procedure I)

In a nitrogen glove box, a dry screw-capped vial with a magnetic stirrer bar was charged with metal–base (0.01 mmol, 10 mol%), indole (11.7 mg, 0.10 mmol, 1.00 equiv), **22** (18.1 mg, 0.10 mmol, 1.00 equiv) and THF (0.5 ml). The reaction mixture was stirred at 30 ^{o}C for 16 h. The internal standard, dibenzyl ether, was added prior to ^{1}H NMR analysis of an aliquot of the reaction mixture. For reactions which gave no reaction the mixture was heated to 80 ^{o}C for 63 h and ^{1}H NMR analysis repeated.

Lewis acid addition to the catalytic system (general procedure II)

In a nitrogen glove box, a dry screw-capped vial with a magnetic stirrer bar was charged with metal base (0.01 mmol, 10 mol%), Lewis acid co-catalyst (0.01 mmol, 10 mol%), indole (11.7 mg, 0.10 mmol, 1.00 equiv), **22** (18.1 mg, 0.10 mmol, 1.00 equiv) and THF (0.5 ml). The reaction mixture was stirred at 30 ^{o}C for 16 h. The internal standard, dibenzyl ether, was added prior to ^{1}H NMR analysis of an aliquot of the reaction mixture.

Amine protecting groups for the 3-component reaction (general procedure III)

In a dry screw-capped vial with a magnetic stirrer bar was charged with Li_2CO_3 (1.50 mg, 0.02 mmol, 5 mol%), CuCl (2.00 mg, 0.02 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.02 mmol, 5 mol%) and 2-MeTHF (200 µL) and stirred at 30 ^{o}C for 1 h. Indole (46.8 mg, 0.40 mmol, 1.00 equiv) was added followed by a solution of benzaldehyde (84.9 mg, 0.80 mmol, 2.00 equiv), and amine (0.80 mmol, 2.00 equiv) in 2-MeTHF (200 µL). The reaction mixture was stirred at 30 ^{o}C for 24 h. The internal standard, dibenzyl ether, was added prior to ^{1}H NMR analysis of an aliquot of the reaction mixture.

Substrate scope for the 3-component reaction (general procedure IV)

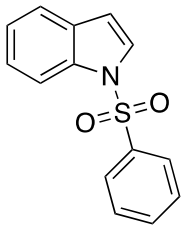
In a dry screw-capped vial with a magnetic stirrer bar was charged with Li_2CO_3 (1.50 mg, 0.02 mmol, 10 mol%), CuCl (2.00 mg, 0.02 mmol, 10 mol%), $NaBF_4$ (2.20 mg, 0.02 mmol, 10 mol%) and 2-MeTHF (100 µL) and stirred at 30 ^{o}C for 1 h. Indole (46.8 mg, 0.40 mmol, 1 equiv) was added followed by a solution of aldehyde (0.80 mmol, 2.00 equiv), and *o*-anisidine (49.2 mg, 0.80 mmol, 2.00 equiv) in 2-MeTHF (100 µL). The reaction mixture was stirred at 30 ^{o}C for 24 h. The internal standard, dibenzyl ether, was added prior to ^{1}H NMR analysis of an aliquot of the reaction mixture. The products were purified by PTLC using ethyl acetate:hexanes.

Deuterium labelling and monitoring (general procedure V)

In a dry screw-capped vial with a magnetic stirrer bar was charged with Li_2CO_3 (1.50 mg, 0.02 mmol, 10 mol%), CuCl (2.00 mg, 0.02 mmol, 10 mol%), $NaBF_4$ (2.20 mg, 0.02 mmol, 10 mol%) and 2-MeTHF (200 µL) and stirred at 30 ^oC for 1 h. d-Indole (46.8 mg, 0.40 mmol, 1 equiv) was added followed by 17 (72.5 mg, 0.40 mmol, 1 equiv) in 2-MeTHF (200 µL). The reaction mixture was transferred to an NMR tube and 1H NMR taken at specified intervals using lock off.

3.2.1 Protected indoles

_N_-Benzenesulfonylindole (316)[210]



To a round bottom flask under an atmosphere of argon was added indole (2.00 g, 17.0 mmol, 1.00 equiv), NaOH (20 ml, 50% aq), toluene (30 ml) and water (15 ml). TBAB (0.64 g, 2.00 mmol, 0.12 equiv) was added followed by benzene sulfonyl chloride (3.00 g 17.0 mmol, 1.00 equiv) and the mixture stirred vigorously for 14 h. The reaction mixture was extracted with diethyl ether (3 x 30 ml) and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford an amorphous solid which was recrystallised from ethanol and dried *in vacuo* to afford the titled compound.

Colourless solid

Yield: 2.10 g (48%).

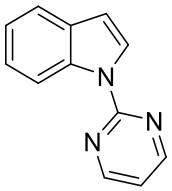
Mp: 78.2–79.3 °C (Lit.: 78–79 °C).[211]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 7.3 Hz, 2H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.56–7.53 (m, 2H), 7.47–7.44 (t, *J* = 7.9 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.25 (t, *J* = 7.9 Hz, 1H), 6.69 (d, *J* = 3.6 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9, 134.5, 133.5, 130.4, 128.9 (2C), 126.4 (2C), 126.0, 124.3, 123.1, 121.1, 113.2, 108.9 ppm.

IR (neat)**:** ν = 3152, 1447, 1360, 1175, 1135, 991, 725 cm^{-1}.

_N_-pyrimidylindole (46)[212]



To a solution of indole (351 mg, 3.00 mmol, 1.00 equiv) in DMF (10 ml) was added portion wise NaH (86.4 mg, 3.60 mmol, 1.20 equiv). After 1 h 2-chloropyrimidine (412 mg, 3.60 mmol, 1.20 equiv) was added. Stirring was continued for 18 h after which water (15 ml) was added and extracted with ethyl acetate (3 x 15 ml). The combined organic layer was dried over $MgSO_4$ and the solvent removed *in vacuo* yielding a colourless crystalline solid which was

dissolved in THF, dried over molecular sieves (4 Å), filtered and the solvent removed under reduced pressure.

Colourless solid

Yield: 350 mg (60%).

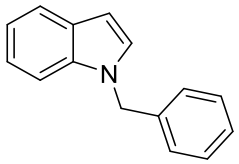
Mp: 84.5–85.3 °C (Lit.: 85–86 °C).[212]

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (dq, *J* = 8.4, 0.9 Hz, 1H), 8.73 (d, *J* = 4.8 Hz, 2H), 8.31 (d, *J* = 3.7 Hz, 1H), 7.69–7.61 (m, 1H), 7.38 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.31–7.22 (m, 1H), 7.07 (t, *J* = 4.8 Hz, 1H), 6.74 (dd, *J* = 3.7, 0.8 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.1 (2C), 157.9, 135.4, 131.4, 125.8, 123.7, 122.1, 120.8, 116.3, 116.1, 106.9 ppm.

IR (neat)**:** ν = 3138, 3049, 1564, 1450, 1427, 1204, 970, 748 cm^{-1}.

***N*-Benzylindole (317)[213]**



To a dispersion of NaH (288 mg, 12.0 mmol, 1.20 equiv) in THF (20 ml) at 0 °C was added indole (1.17 g, 10.0 mmol, 1.00 equiv) dissolved in THF (10 ml) and the mixture stirred for 1 h. Benzyl bromide (1.79 ml, 15.0 mmol, 1.50 equiv) was added dropwise and the solution stirred for 4 h. The reaction was quenched with ammonium chloride (10 ml) and the solution extracted with ethyl acetate (3 x 20 ml). The combined organic fractions were washed with brine (20 ml) and dried over magnesium sulfate and the solvent removed *in vacuo*. The solid was purified by column chromatography eluting 20% ethyl acetate in hexane.

Pale pink solid

Yield: 1.82 g (88%).

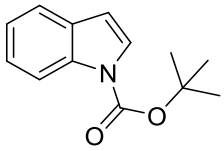
Mp: 42.5–43.0 °C (Lit.: 42–43 °C).[213]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 7.5 Hz, 1H), 7.36–7.31 (m, 3H), 7.31–7.27 (m, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.18–7.13 (m, 4H), 6.60 (d, *J* = 3.0 Hz, 1H), 5.36 (s, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.6, 136.4, 128.8 (2C), 128.7, 128.3, 127.6, 126.8 (2C), 121.7, 121.0, 119.6, 109.7, 101.7, 50.1 ppm.

IR (neat)**:** ν = 3024, 1462, 1317, 1179, 119, 714 cm^{-1}.

***Tert*-butyl-*N*-indolecarboxylate (<u>318</u>)[214]**



Indole (293 mg, 2.50 mmol, 1.00 equiv) was dissolved in DCM (5 ml). To the solution DMAP (61.1 mg, 0.50 mmol, 0.20 equiv) and NEt_3 (758 mg, 7.50 mmol, 3.00 equiv) was added and the resultant mixture stirred for 1 h at ambient temperature. Di-*tert*-butyl dicarbonate (600 mg, 2.75 mmol, 1.10 equiv) was added and the reaction stirred for 3 h at ambient after which the reaction was quenched with water (10 ml) and extracted with DCM (3 x 5 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure; drying *in vacuo* afforded the crude product as a colourless liquid which was suitably pure.

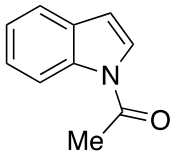
Colourless liquid

Yield: 530 mg (97%)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.3 Hz, 1H), 7.62 (d, *J* = 3.7 Hz, 1H), 7.58 (ddd, *J* = 7.8, 1.3, 0.8 Hz, 1H), 7.37–7.30 (m, 1H), 7.25 (ddd, *J* = 7.8, 7.2, 1.3 Hz, 1H), 6.59 (dd, *J* = 3.7, 0.8 Hz, 1H), 1.70 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.8, 135.2, 130.6, 125.9, 124.2, 122.6, 120.9, 115.2, 107.3, 83.6, 28.2 (3C) ppm.

***N*-Acetylindole (<u>319</u>)[215]**



To a solution of indole (1.20 g, 10.2 mmol, 1.00 equiv) in DCM (100 ml) at ambient temperature was added tetrabutylhydrogen sulfate (340 mg, 10.4 mmol, 1.02 equiv) and sodium hydroxide 2.00 g, 51.0 mmol, 5.00 equiv) and the mixture stirred for 0.5 h. Acetyl chloride (2.37 g, 30.6 mmol, 3 equiv) was added and the mixture stirred at ambient for 2 h afterwhich water (20 ml) was added cautiously. The organic layer was separated and the aqueous extracted with DCM (3 x 20 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure affording the crude compound as an oil which was purified using column chromatography eluting ethyl acetate: hexane(1:4)

dissolved in THF and dried over 4 Å molecular sieves for 18 h. The solution was then filtered and the solvent removed under reduced pressure and finally dried *in vacuo*.

Colourless oil.

Yield: 780.0 mg (48%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (s, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.42–7.37 (m, 1H), 7.34 (t, *J* = 8.4 Hz, 1H), 7.27 (dd, *J* = 7.8, 1.0 Hz, 1H), 6.63 (d, *J* = 3.8 Hz, 1H), 2.63 (s, 3H) ppm.

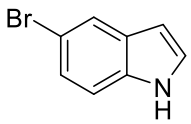
^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 135.2, 130.1, 124.9, 124.8, 123.4, 120.5, 116.2, 108.9, 23.7 ppm.

IR (neat)**:** ν = 3051, 1697, 1450, 1319, 1207, 932, 746 cm^{-1}.

MS (ESI): calculated for $C_{10}H_9NOK^+$ = [M+K^+]: *m*/*z* = 198.2, found: *m*/*z* = 198.2.

3.2.2 Synthesis of Indoles

5-Bromoindole (320)[216]



A solution of Sodium 1-Acetylindoline-2-sulfonate hemihydrate (12.0 g, 44.0 mmol, 1.00 equiv) in water (55 ml) was cooled to 0 °C and bromine (7.75 g, 48.5 mmol, 1.10 equiv) was added cautiously dropwise. The mixture was stirred for 1 h then warmed to ambient temperature and stirred for an additional hour. Sodium bisulfite (75 ml, sat aq.) was added followed by NaOH (7.50 g, 187.5 mmol, 4.30 equiv) and the mixture refluxed overnight. The mixture was cooled and the solid formed filtered under vacuum to afford a brown solid. Recrystalisation from ether yielded a tan solid which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Tan solid

Yield: 3.20 g (37%).

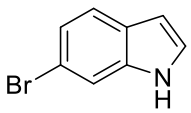
Mp: 91.5–92.0 °C (Lit.: 90–92 °C).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (br s, 1H), 7.77–7.76 (m, 1H), 7.28–7.26 (m, 1H), 7.26–7.25 (m, 1H), 7.19 (t, *J* = 3.1 Hz, 1H), 6.49 (ddd, *J* = 3.1, 2.1, 0.8 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.1, 129.3, 125.1, 124.6, 122.9, 112.7, 112.1, 102.0 ppm.

IR (neat)**:** ν = 3410, 1560, 1441, 1314, 1090, 881, 762 cm^{-1}.

6-Bromoindole (321)[217]



To 4-bromo-2-nitrotoluene (2.00 g, 9.20 mmol, 1.00 equiv) was added anhydrous DMF (40 ml), *N, N* dimethylformamide dimethylacetal (1.60 ml, 11.2 mmol, 1.20 equiv) and pyrrolidine (1.00 ml, 11.2 mmol, 1.20 equiv). The mixture was heated at reflux until tlc indicated consumption of the starting material. The mixture was cooled to 0 °C before addition of ammonium acetate (40 ml, 4M) and $TiCl_3$ (43.0 ml, 15% in 10% HCl). The mixture was stirred for 1 h. The grey slurry was gradually brought to ambient temperature and NaOH (4M) was added to bring the solution to pH 9. The solution was extracted with diethyl ether (3 x 100 ml) and the combined organic extracts were washed with brine (100 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure. Recrystalisation from

hexanes yielded a tan solid which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Tan solid

Yield: 1.25 g (70%).

Mp: 92.6–93.2 °C (Lit.: 92–93 °C).[218]

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (br s, 1H), 7.56–7.55 (m, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.22 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.19 (dd, *J* = 3.2, 2.4 Hz, 1H), 6.53 (ddd, *J* = 3.2, 2.1, 0.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.6, 126.7, 124.7, 123.2, 121.9, 115.5, 113.9, 102.9 ppm.

IR (neat)**:** ν = 3393, 1605, 1335, 1093, 891, 806, 729 cm^{-1}.

Allyl Bromide (322) [219]

KOH (19.6 g, 350 mmol, 1.30 equiv) was dissolved in ethanol (110 ml). To the flask was attached a still head, condenser and receiver flask and a pressure equalising dropping funnel. The solution was brought to 40 °C and 1, 2 dibromoethane (49.9 g, 22.7 ml, 266 mmol, 1.00 equiv) was added steadily dropwise. After addition was complete the solution was heated for a further 1 h collecting the distillate at -78 °C. The allyl bromide was distilled a further time.

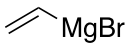
Colourless liquid

Yield: 10.10 g (36%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.47 (dd, *J* = 7.9, 7.2 Hz, 1H), 6.01 (dd, *J* = 7.2, 1.9 Hz, 1H), 5.88 (dd, *J* = 7.9, 1.9 Hz, 1H) ppm.

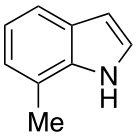
^{13}C NMR (125 MHz, $CDCl_3$): δ = 121.88, 113.97 ppm.

Vinyl magnesium bromide[220]



THF (60 ml) was added to magnesium turnings (3.30 g, 135 mmol, 1.28 equiv) and the flask placed under argon and cooled to 0 °C. Iodine (1 crystal) was added followed by vinyl bromide (11.4 g, 106 mmol, 1.00 equiv) in THF (40 ml). The flask was stirred for 2 h and the Grignard titrated[221] and stored under argon for further use.

7-Methylindole (323)[222]



To a solution of *o*-nitrotoluene (4.11 g, 30.0 mmol, 1.00 equiv) in THF (100 ml) cooled to -40 ^{o}C was added vinyl magnesium bromide (100 ml, 1.00 M, 100 mmol, 3.30 equiv). The solution was allowed to warm to ambient and stirred for 15 h. Ammonium chloride (50 ml, sat. aq.) was added and the mixture extracted with ether (3 x 100 ml). The combined organic fractions were dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The solid obtained was purified by flash column chromatography eluting EtOAc: hexane (1:10).

Colourless solid

Yield: 1.20 g (34%).

Mp: 77.3–77.9 ^{o}C

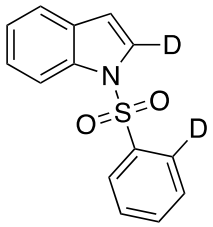
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09 (br s, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.25 (t, *J* = 2.8 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 7.03–7.04 (m, 1H), 6.60 (dd *J* = 2.8 Hz, 1H), 2.54 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.4, 127.4, 123.8, 122.5, 120.2, 120.0, 118.5, 103.2, 16.7 ppm.

IR (neat)**:** ν = 3707, 2966, 2864, 1483, 1054 cm^{-1}.

3.2.3 Deuterated indoles

2-Deuterio-1-(2-deuteriophenyl)sulfonyl-indole (324)[223]



N-benzenesulfonylindole (3.00 g, 12 mmol, 1.00 equiv) was stirred at -78 °C in THF (60 ml). ^{n}BuLi (9.6 ml, 24 mmol, 2.00 equiv, 2.5 M) was added and the solution warmed to ambient and stirred for 2 h. The solution was recooled to -78 °C and D_2O (3 ml) was added and the mixture stirred at ambient for 30 min. Solid potassium carbonate (1 g) and MTBE (100 ml) added and the mixture filtered and dried under reduced pressure. The formed amorphous solid was crystallised twice from MTBE.

Colourless solid.

Yield: 1.57 g (51%).

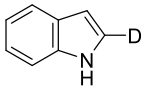
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (dq, *J* = 8.4, 0.8 Hz, 1H), 7.88 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.57–7.49 (m, 2H), 7.48–7.39 (m, 2H), 7.34–7.27 (m, 1H), 7.25–7.20 (m, 1H), 6.66 (t, *J* = 0.7 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9, 134.5, 133.5, 130.5, 129.0, 128.9, 126.5, 126.0 (t, *J* = 25.9 Hz), 124.4, 123.1, 121.1, 113.2, 108.8 ppm.

^{2}H NMR (77 MHz, $CDCl_3$): δ = 7.92, 7.60 ppm

IR (neat)**:** ν = 3067, 2359, 1437, 1364, 1128, 827, 749, 717 cm^{-1}.

2-Deuterio-indole (<u>140</u>)[223]



2-Deuterio-1-(2-deuteriophenyl)sulfonyl-indole (1.00 g, 3.86 mmol, 1.00 equiv) was dissolved in methanol (11 ml) and NaOH (14 ml, 2M) added and the mixture refluxed for 16 h. The solvent was removed in vacuo and the solid extracted with MTBE (3 x 20 ml) dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. The solid was recrystalised twice from hexanes.

Colourless solid.

Yield: 400 mg (88%).

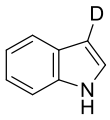
Mp: 51.7–52.0 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 7.65 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.40 (dq, *J* = 7.7, 0.9 Hz, 1H), 7.23–7.17 (m, 1H), 7.12 (ddd, *J* = 8.2, 7.1, 1.0 Hz, 1H), 6.59–6.54 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.8, 127.9, 123.8 (t, *J* = 28.0 Hz), 122.0, 120.7, 119.8, 111.0, 102.7 ppm.

^{2}H NMR (77 MHz, $CDCl_3$): δ = 7.28 ppm.

3-Deuterioindole (136)[224]



Indole (2.00 g, 17.0 mmol, 1.00 equiv) was suspended in DCl (0.01 M, 20 ml) and stirred at 60 °C for 3 h. The reaction was cooled and extracted with MTBE (3 x 20 ml) and the combined organic layers dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure affording a tar. The tar was redissolved in MTBE (20 ml) and H_2O (10 ml) added and stirred for 0.5 h. The organic layer was separated and the aqueous further extracted with MTBE (2 x 20 ml). The combined organic layers were dried over magnesium sulfate, filtered, and dried to a tar which was recrystalised from hexanes.

Colourless solid.

Yield: 1.57 g (78%).

Mp: 51.0–51.5 °C

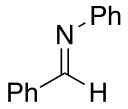
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (s, 1H), 7.65 (dq, *J* = 7.9, 0.9 Hz, 1H), 7.41 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.23–7.21 (m, 1H), 7.20–7.17 (m, 1H), 7.12 (dd, *J* = 7.9, 0.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.4, 127.6, 123.8, 121.7 (d, *J* = 1.4 Hz), 120.5, 119.5, 110.7, 102.3 (d, *J* = 22.7 Hz) ppm.

IR (neat)**:** ν = 3393, 2974, 1620, 1454, 1065, 739 cm^{-1}.

3.2.4 Other starting materials

_N_-Phenyl-Benzaldimine (22)[225]



In an oven dried flask under an argon atmosphere, aniline (4.66 g, 50.0 mmol, 1.00 equiv) and benzaldehyde (5.30 g, 10.0 mmol, 1.00 equiv) were combined. Ethanol (25 mL) and magnesium sulfate (10 g) were added and the mixture stirred for 15 h. The mixture was then filtered, and the solvent removed under reduced pressure to give the crude imine, which was recrystallized twice from refluxing ethanol to yield the pure aldimine. The compounds were then further dried over 4 Å MS in THF, dried *in vacuo* and ground before use.

Pale yellow solid

Yield: 8.20 g (90%).

Mp: 52.0–52.3 °C (Lit.: 51–52 °C).

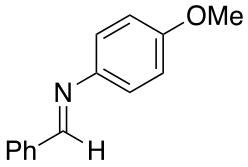
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.50 (s 1H), 7.96 (dd, *J* = 6.5, 3.1 Hz, 2H), 7.51–7.44 (m, 3H), 7.40–7.36 (m, 2H), 7.24–7.18 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.5, 152.1, 136.2, 131.5, 129.2 (2C), 128.9 (2C), 128.8 (2C), 126.0, 120.9 (2C) ppm.

IR (neat)**:** ν = 3061, 2889, 1624, 1192, 754, 690 cm^{-1}.

MS (ESI): calculated for $C_{13}H_{11}N^+$ = [M+H$^+$]: *m*/*z* = 182.2, found: *m*/*z* = 182.2.

(*E*)-*N*-(4-methoxyphenyl)-1-phenyl-methanimine (325)[226]



In an oven dried flask under an argon atmosphere, *p*-anisidine (6.16 g, 50.0 mmol, 1.00 equiv) and benzaldehyde (5.30 g, 10.0 mmol, 1.00 equiv) were combined. Ethanol (25 mL) and magnesium sulfate (10 g) were added and the mixture stirred for 15 h. The mixture was then filtered, and the solvent removed under reduced pressure to give the crude imine, which was recrystallized twice from refluxing ethanol to yield the pure aldimine. The compounds were then further dried over 4 Å MS in THF, dried *in vacuo* and ground before use.

Pale pink solid

Yield: 6.25 g (59%).

Mp: 71.0–71.5 °C (Lit.: 69–70 °C).

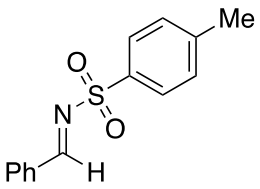
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.48 (s, 1H), 7.90–7.88 (m, 2H), 7.47–7.46 (m, 3H), 7.26–7.23 (m, 2H), 6.94–6.92. (m, 2H), 3.83 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4, 158.3, 144.9, 136.5, 131.0, 128.7 (2C), 128.6 (2C), 122.2 (2C), 114.7 (2C), 55.5 ppm.

IR (neat)**:** ν = 2955, 1622, 1502, 1244, 1030, 833, 687 cm^{-1}.

MS (ESI): calculated for $C_{14}H_{13}NO^+$ = [M+H$^+$]: *m*/*z* = 211.9, found: *m*/*z* = 211.9.

N-(*p*-toluenesulfonyl)-Benzaldimine (326)[218]



In an oven dried flask under an argon atmosphere, *p*-toluenesulfonylamide (8.56 g, 50.0 mmol, 1.00 equiv) and benzaldehyde (5.30 g, 10.0 mmol, 1.00 equiv) were combined. Ethanol (25 mL) and magnesium sulfate (10 g) were added and the mixture stirred for 15 h. The mixture was then filtered, and the solvent removed under reduced pressure to give the crude imine, which was recrystallized twice from refluxing ethanol to yield the pure aldimine. The compounds were then further dried over 4 Å MS in THF, dried *in vacuo* and ground before use.

Colourless solid

Yield: 7.30 g (56%).

Mp: 113.5–114.0 °C (Lit.: 112–114 °C).

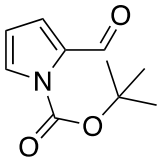
^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.03 (s, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.89 (d, *J* = 8.5 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 2H), 2.44 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 144.6, 135.1, 134.9, 132.4, 131.3 (2C), 129.8 (2C), 129.2 (2C), 128.1 (2C), 21.7 ppm.

IR (neat)**:** ν = 3071, 1595, 1318, 1153, 1086, 781, 638 cm^{-1}.

MS (ESI): calculated for $C_{14}H_{14}NO_2S^+$ = [M+H$^+$]: *m*/*z* = 260.3, found: *m*/*z* = 260.0.

N-tert-butoxycarbonyl-pyrrole-2-carboxylate (327)[227]



To a solution of pyrrole-2-carboxaldehyde (951 mg, 10.0 mmol, 1.00 equiv) in DCM (50 ml) was added di-*tert*-butyl dicarbonate (2.40 g, 11.0 mmol, 1.10 equiv), DMAP (61.0 mg, 0.50

mmol, 0.05 equiv), and triethylamine (1.01 g, 10.0 mmol, 1.00 equiv). The reaction was stirred for 1 h at ambient temperature. The solution was washed with water (10 ml) followed by HCl (3 x 10 ml, 20%). The organic layer was separated and washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*.

Pale brown liquid

Yield: 1.90 g (97%).

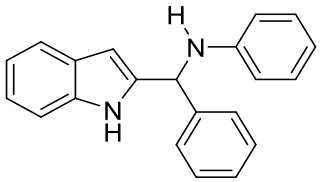
^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.23 (s, 1H), 7.65–7.61 (m, 1H), 7.39–7.35 (m, 1H), 6.59–6.54 (m, 1H), 1.62 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 184.8, 147.1, 131.9, 124.8, 123.0, 113.8, 84.1, 22.8 (3C) ppm.

IR (neat)**:** ν = 2980, 1743, 1665, 1296, 1119, 845, 744 cm^{-1}.

3.2.5 Products of the indole coupling.

_N_-[1H-indol-2-yl)-phenyl-methyl] aniline (25)



25 was prepared according to *general procedure II* using indole (23.4 mg, 0.20 mmol, 1.00 equiv), phenyl imine (36.2 mg, 0.20 mmol, 1.00 equiv) in the presence of KHMDS (4.00 mg, 0.01 mmol, 10 mol%) and CuOTf•tol (10.90 mg, 0.01 mmol, 10 mol%) inTHF (200 µL, 1 M), at 30 °C for 15 h. 25 was purified by PTLC on silica gel (EtOAc/NEt_3/PE = 9:1:90; *eluted twice*)

Pale pink solid.

Mp: 68.5–70.0 °C

Yield: 21.5 mg, (36%).

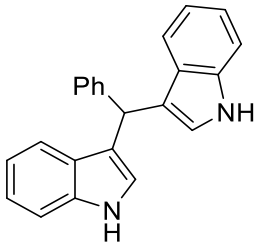
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (s, 1H), 7.63–7.60 (m, 1H), 7.57–7.51 (m, 2H), 7.44–7.34 (m, 4H), 7.27–7.22 (m, 1H), 7.17–7.11 (m, 3H), 6.85–6.76 (m, 1H), 6.73–6.70 (m, 1H), 6.63 (s, 1H), 6.62 (s, 1H), 5.86 (s, 1H) 4.40 (br s, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.9, 136.5, 128.3 (2C), 128.0 (2C), 127.1, 126.1 (2C), 126.0, 123.4, 121.7 (2C), 119.8 (2C), 119.4, 119.2 (2C), 110.9, 110.7, 40.0 ppm.

IR (neat): ν = 3406, 3080, 1599, 1454, 1314, 1093, 870, 733 cm^{-1}.

HRMS (ESI): calculated for $C_{21}H_{18}N_2^+$ = [M^+]: *m*/*z* = 298.1465, found: *m*/*z* = 298.1478.

3, 3'-bisindolyl(phenyl)methane(24) [228]



24 was prepared according to *general procedure II* using indole (23.4 mg, 0.20 mmol, 1.00 equiv), phenyl imine (36.2 mg, 0.20 mmol, 1.00 equiv) in the presence of KHMDS (4.00 mg, 0.01 mmol, 10 mol%) and CuOTf•tol (10.90 mg, 0.01 mmol, 10 mol%) inTHF (200 µL, 1 M), at 30 °C for 15 h. 24 was purified by PTLC on silica gel (EtOAc/NEt_3/PE = 9:1:90; *eluted twice*)

Pink solid.

Yield: 25.0 mg, (38%).

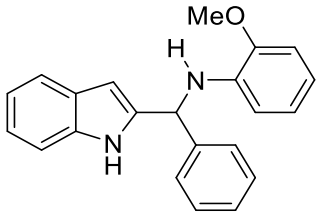
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (s, 2H), 7.43 (dq, *J* = 7.9, 0.9 Hz, 2H), 7.41–7.36 (m, 3H), 7.34–7.28 (m, 3H), 7.27–7.22 (m, 1H), 7.20 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 2H), 7.04 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 2H), 6.69 (dd, *J* = 2.4, 1.1 Hz, 2H), 5.96 (s, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 147.9, 142.9, 136.8, 129.3 (2C), 128.7 (2C), 127.4 (2C), 126.2 (2C), 123.6, 122.5 (2C), 120.0, 119.5 (2C), 119.0, 117.5, 115.3, 113.5, 111.6, 55.9 ppm.

IR (neat): ν = 3406, 3055, 2918, 1599, 1491, 1454, 1416, 1240, 1091, 792 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{18}N_2^+$ = [M^+]: *m*/*z* = 321.1362, found: *m*/*z* = 321.1362.

2-Methoxy-*N*-[(1H-indol-2-yl)-phenyl-methyl]aniline (71)



71 was prepared according to *general procedure IV* using indole (23.4 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and benzaldehyde (42.9 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 71 was purified by PTLC on silica gel ($EtOAc/NEt_3$/PE = 9:1:90; *eluted twice*).

Colourless solid.

Yield: 61.4 mg, (92%).

Mp: 133–134 °C

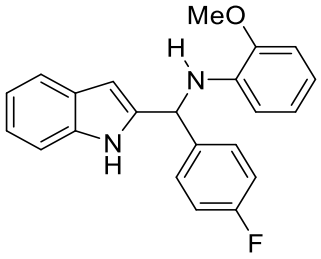
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (br s, 1H), 7.63 (d, *J* = 8.9 Hz, 1H), 7.54 (d, *J* = 7.1 Hz, 1H), 7.42–7.35 (m, 2H), 7.33–7.27 (m, 2H), 7.24 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.13 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.88–6.83 (m, 2H), 6.82 (d, *J* = 1.4 Hz, 1H), 6.79 (td, *J* = 7.7, 1.4 Hz, 1H), 6.69 (td, *J* = 7.7, 1.6 Hz, 1H), 6.56 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.85 (s, 1H), 4.99 (s, 1H), 3.84 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.78, 142.88, 137.64, 136.64, 128.50 (2C), 127.33 (2C), 127.08, 126.19, 123.30, 122.32, 121.18, 119.75, 119.54, 119.21, 116.45, 111.21, 111.10, 109.35, 55.61, 55.42 ppm.

IR (neat): ν = 3381, 3059, 1599, 1506, 1221, 1123, 1028, 731 cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{20}N_2ONa^+$ = [M+Na^+]: *m*/*z* = 351.1465, found: *m*/*z* = 351.1453.

2-((2-methoxyphenyl)-4-fluorobenzylidene) indole (74)



74 was prepared according to *general procedure IV* using indole (23.4 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and *p*-fluorobenzaldehyde (49.6 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 74 was purified by PTLC on silica gel (EtOAc/NEt_3/PE = 9:1:90; *eluted thrice*).

Tan solid

Yield: 60.3 mg, (88%).

Mp: 89–90 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.02 (br s, 1H), 7.59 (d, *J* = 8.0, 0.9 Hz, 1H), 7.56–7.46 (m, 2H), 7.40 (dt, *J* = 8.2, 0.8 Hz, 1H), 7.24 (ddt, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.12 ddd (*J* = 8.0, 7.1, 1.0 Hz, 1H), 7.07–7.02 (m, 2H), 6.84–6.75 (m, 3H), 6.70 (td, *J* = 7.7, 1.6 Hz, 1H), 6.52 (dd, *J* = 7.9, 1.4 Hz, 1H), 5.83 (s, 1H), 4.96 (br s, 1H), 3.84 (s, 3H) ppm.

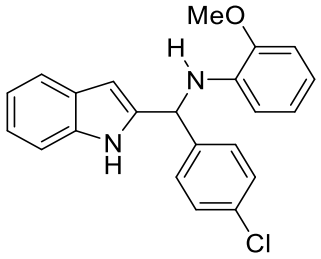
^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.0 (d, *J* = 244.8 Hz), 146.8, 138.6, 137.4, 136.7, 128.8 (d, *J* = 8.0 Hz, 2C), 123.2, 124.4, 121.2, 119.8, 119.5, 119.1, 118.5, 116.7, 115.3 (d, *J* = 21.4 Hz, 2C), 111.2, 111.1, 109.4, 55.4, 55.0 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -116.0 (ap. tt, *J* = 8.7, 5.3 Hz) ppm.

IR (neat): ν = 3431, 3379, 2927, 2360, 1600, 1504, 1221, 1123, 736 cm^{-1}

HRMS (EI): calculated for $C_{22}H_{19}FNO_2Na^+$ = [M+Na$^+$]: *m*/*z* = 369.1374, found: *m*/*z* = 369.1363.

2-((2-methoxyphenyl)-4-chlorobenzylidene) indole (75)



75 was prepared according to *general procedure IV* using indole (23.4 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and *p*-chlorobenzaldehyde (56.2 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components,

in 2-MeTHF (200 µL, 1 M), at 30 °C for 62 h. 75 was purified by PTLC on silica gel (EtOAc/PE = 10:90; *eluted thrice*).

Colourless solid.

Yield: 56.4 mg, (78%).

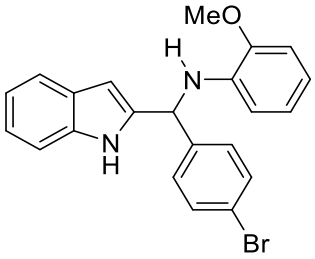
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.46–7.42 (m, 2H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.31–7.28 (m, 2H), 7.21 (td, *J* = 7.6, 1.1 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H), 6.81–6.78 (m, 2H), 6.75 (td, *J* = 7.7, 1.4 Hz, 1H), 6.69–6.64 (m, 1H), 6.46 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.78 (s, 1H), 4.92 (br s, 1H), 3.80 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.8, 141.5, 137.4, 136.6, 132.7, 128.7 (4C), 126.0, 123.3, 122.5, 121.2, 119.9, 119.4, 118.8, 116.8, 111.3, 111.1, 109.4, 55.4, 55.0 ppm.

IR (neat): ν = 3412, 2916, 2361, 1601, 1508, 1221, 907, 731 cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{19}ClN_2ONa^+$ = [M^+]: *m*/*z* = 385.1078, found: *m*/*z* = 385.1097.

2-((2-methoxyphenyl)-4-bromobenzylidene) indole (<u>76</u>)



76 was prepared according to *general procedure IV* using indole (23.4 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and *p*-bromobenzaldehyde (74.0 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 76 was purified by PTLC on silica gel (EtOAc /PE = 20:80; *eluted thrice*).

Colourless solid.

Yield: 66.8 mg, (82%).

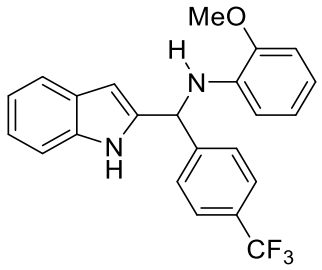
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05 (s, 1H), 7.60 (dq, *J* = 8.0, 1.0 Hz, 1H), 7.52–7.45 (m, 2H), 7.45–7.37 (m, 3H), 7.24 (ddd, *J* = 8.3, 7.1, 1.2 Hz, 1H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.86–6.74 (m, 3H), 6.69 (td, *J* = 7.7, 1.6 Hz, 1H), 6.49 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.79 (s, 1H), 4.95 (s, 1H), 3.83 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.4, 146.8, 142.3, 140.1, 137.3, 129.7, 128.8 (2C), 127.4, 127.3, 126.1, 125.3, 124.9, 122.4, 121.2, 121.1, 116.9, 111.9, 111.2, 109.4, 55.5, 55.4 ppm.

IR (neat): ν = 3412, 2926, 2363, 1599, 1508, 1223, 1009, 737 cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{19}BrN_2ONa^+$ = [M+Na^+]: *m*/*z* = 429.0573, found: *m*/*z* = 429.0579.

2-((2-methoxyphenyl)-4-trifluoromethylbenzylidene) indole (77)



77 was prepared according to *general procedure IV* using indole (23.4 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and *p*-trifluoromethylbenzaldehyde (69.6 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 77 was purified by PTLC on silica gel (EtOAc/PE = 1:5; *eluted twice*).

Colourless solid.

Yield: 59.2 mg, (75%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (br s, 1H), 7.65–7.61 (m, 2H), 7.61–7.56 (m, 3H), 7.39–7.36 (m, 1H), 7.24–7.20 (m, 1H), 7.11 (ddd, *J* = 8.0, 7.1, 0.9 Hz, 1H), 6.81–6.74 (m, 3H), 6.68 (td, *J* = 7.6, 1.6 Hz, 1H), 6.43 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.86 (s, 1H), 4.97 (br s, 1H), 3.81 (s, 3H) ppm.

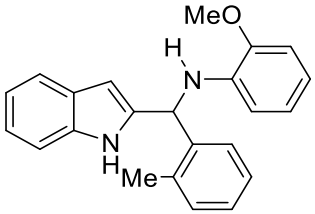
^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.9, 142.4, 138.0, 137.4, 128.4 (2C), 127.4, 127.3 (2C), 125.5, 125.4 (q, *J* = 271.0 Hz), 125.0, 122.3 (q, *J* = 31.8 Hz), 121.1, 120.2, 119.2 (q, *J* = 3.5 Hz), 117.3 (q, *J* = 4.3 Hz), 116.9, 111.5, 111.3, 109.5, 55.6, 55.4 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -62.29 ppm

IR (neat): ν = 3410, 2916, 1600, 1508, 1323, 1123, 739 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{19}F_3N_2ONa^+$ = [M+Na^+]: *m*/*z* = 419.1342, found: *m*/*z* = 419.1349.

2-((2-methoxyphenyl)-2-methylbenzylidene) indole (72)



72 was prepared according to *general procedure IV* using indole (23.4 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and *o*-tolualdehyde (48.1 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF

(200 µL, 1 M), at 30 °C for 15 h. 72 was purified by PTLC on silica gel (EtOAc/PE = 20:80; *eluted twice*).

Tan solid.

Yield: 60.5 mg, (88%).

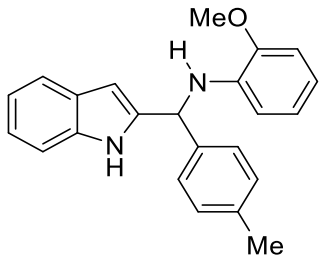
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (s, 1H), 7.62 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.60–7.55 (m, 1H), 7.40 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.28–7.18 (m, 4H), 7.13 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.88–6.80 (m, 2H), 6.72 (dd, *J* = 2.5, 0.9 Hz, 1H), 6.67 (td, *J* = 7.7, 1.6 Hz, 1H), 6.43 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.99 (s, 1H), 4.91 (s, 1H), 3.84 (s, 3H), 2.37 (d, *J* = 0.6 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.7, 140.4, 137.6, 136.7, 135.8, 130.5, 126.9, 126.6, 126.5, 126.2, 123.8, 122.3, 121.2, 119.7, 119.4, 118.0, 116.3, 111.2, 110.7, 109.4, 55.4, 52.0, 19.1 ppm.

IR (neat): ν = 3410, 3059, 2916, 1599, 1506, 1456, 1221, 1026, 735 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{22}N_2ONa^+$ = [M+Na^+]: *m*/*z* = 365.1624, found: *m*/*z* = 365.1600.

2-((2-methoxyphenyl)-4-methylbenzylidene) indole (<u>73</u>)



73 was prepared according to *general procedure IV* using indole (23.4 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and *p*-methylbenzaldehyde (48.0 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 73 was purified by PTLC on silica gel (EtOAc/PE = 10:90; *eluted twice*).

Colourless solid.

Yield: 48.4 mg, (71%).

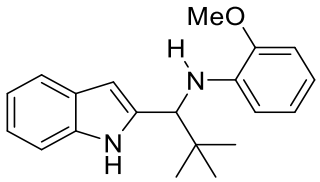
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (br s, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.40–7.32 (m, 3H), 7.19 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.10–7.05 (m, 1H), 6.84 (s, 1H), 6.81–6.70 (m, 2H), 6.63 (td, *J* = 7.7, 1.6 Hz, 1H), 6.52 (dd, *J* = 7.9, 1.6 Hz, 1H), 5.79 (s, 1H), 4.92 (br s, 1H), 3.80 (s, 3H), 2.33 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.7, 139.9, 137.7, 136.7, 136.6, 129.2 (2C), 127.2 (2C), 126.2, 123.2, 122.3, 121.2, 119.7, 119.6, 119.3, 116.3, 111.2, 111.1, 109.3, 55.4, 29.7, 21.1 ppm.

IR (neat): ν = 3412, 2916, 2849, 1599, 1508, 1221, 907, 738 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{22}N_2ONa^+$ = [M+Na^+]: *m*/*z* = 365.1624, found: *m*/*z* = 365.1593.

2-Methoxy-*N*-[(1H-indol-2-yl)-*tert*butyl-methyl]aniline (87)



87 was prepared according to *general procedure IV* using indole (23.4 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and *tert*-butylaldehyde (34.4 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 87 was purified by PTLC on silica gel (EtOAc/PE = 10:90; *eluted twice*).

Colourless oil.

Yield: 41.2 mg, (67%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (br s, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.23–7.12 (m, 2H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.89–6.77 (m, 1H), 6.61 (t, *J* = 7.6 Hz, 1H), 6.57–6.48 (m, 1H), 6.33 (d, *J* = 9.4 Hz, 1H), 4.44 (s, 1H), 3.91 (s, 3H), 3.90 (br s, 1H), 1.11 (s, 9H) ppm.

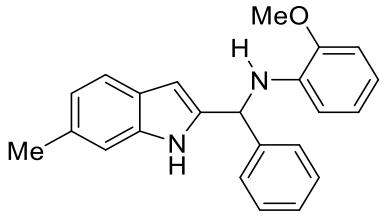
^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.8, 138.2, 128.0, 122.9, 121.5, 121.3 (2C), 119.8, 119.3 (2C), 117.1, 115.6 (2C), 111.1, 110.6, 109.1, 59.9, 55.4, 36.0, 29.7, 27.2 ppm.

IR (neat): ν = 3416, 2916, 2849, 1614, 1506, 1223, 908, 735 cm^{-1}.

HRMS (ESI): calculated for $C_{20}H_{24}N_2ONa^+$ = [M+Na^+]: *m*/*z* = 331.1781, found: *m*/*z* = 331.1777.

3.2.6 Other indole pronucleophiles

2-Methoxy-*N*-[(6-methyl-1H-indol-2-yl)-phenyl-methyl]aniline (<u>106</u>)



106 was prepared according to *general procedure IV* using 6-methylindole (26.2 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and benzaldehyde (42.2 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 22 h. 106 was purified by PTLC on silica gel (EtOAc/PE = 1:90; *eluted twice*).

Colourless solid.

Yield: 58.8 mg (81%).

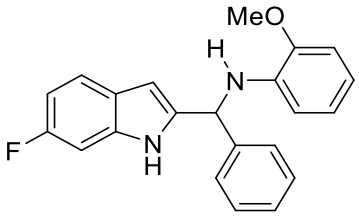
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87 (br s, 1H), 7.49 (d, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.35–7.30 (m, 2H), 7.26–7.23 (m, 1H), 7.16 (s, 1H), 6.92 (dd, *J* = 8.1, 1.0 Hz, 1H), 6.79–6.71 (m, 3H), 6.66–6.61 (m, 1H), 6.50 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.78 (s, 1H), 4.94 (br s, 1H), 3.80 (s, 3H), 2.45 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.8, 142.9, 137.7, 137.1, 132.2, 128.4 (2C), 127.3 (2C), 127.0, 124.0, 122.6, 121.5, 121.1, 119.2, 119.1, 116.3, 111.1, 111.1, 109.3, 55.6, 55.4, 21.7 ppm.

IR (neat): ν = 3414, 2916, 2849, 2359, 1601, 1508, 1223, 907, 729 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{22}N_2ONa^+$ = [M+Na^+]: *m*/*z* = 365.1624, found: *m*/*z* = 365.1601.

2-Methoxy-*N*-[(6-fluoro-1H-indol-2-yl)-phenyl-methyl]aniline (<u>108</u>)



108 was prepared according to *general procedure IV* using 6-fluoroindole (27.0 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and benzaldehyde (42.9 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components,

in 2-MeTHF (200 µL, 1 M), at 30 °C for 24 h. 108 was purified by PTLC on silica gel (EtOAc/NEt_3/PE = 9:1:90; *eluted thrice*).

Light brown solid.

Yield: 53.2 mg (77%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (br s, 1H), 7.55–7.48 (m, 3H), 7.41–7.34 (m, 2H), 7.33–7.29 (m, 1H), 7.05 (dd, *J* = 9.5, 2.2 Hz, 1H), 6.88 (ddd, *J* = 9.6, 8.8, 2.3 Hz, 1H), 6.85–6.78 (m, 2H), 6.73–6.69 (m, 1H), 6.56 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.83 (d, *J* = 4.1 Hz, 1H), 4.97 (br s, 1H), 3.85 (s, 3H) ppm.

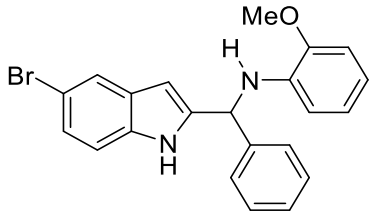
^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.1 (d, *J* = 237.9 Hz), 146.8, 142.7, 137.5, 136.6 (d, *J* = 12.5 Hz), 128.6 (2C), 127.3 (2C), 127.2, 123.5 (d, *J* = 3.5 Hz), 122.8, 121.2, 120.3 (d, *J* = 10.0 Hz), 119.3, 116.6, 111.1, 109.4, 108.5 (d, *J* = 24.4 Hz), 97.5 (d, *J* = 25.9 Hz), 55.6, 55.5 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -120.70 ppm

IR (neat): ν = 3412, 3063, 2916, 1599, 1508, 1242, 906, 733 cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{18}ON_2F^+$ = [M^+]: *m*/*z* = 345.1398, found: *m*/*z* = 345.1385.

2-Methoxy-*N*-[(6-bromo-1H-indol-2-yl)-phenyl-methyl]aniline (<u>109</u>)



109 was prepared according to *general procedure IV* using 5-bromoindole (39.2 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and benzaldehyde (42.5 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 109 was purified by PTLC on silica gel (EtOAc/NEt_3/PE = 9:1:90; *eluted thrice*).

Pale brown solid

Yield: 51.2 mg (63%).

Mp: 163–165 °C

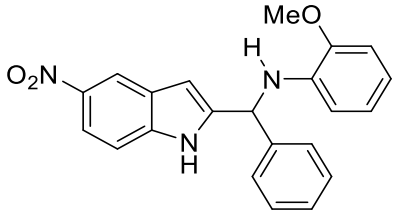
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (br s, 1H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.51–7.47 (m, 2H), 7.37–7.35 (m, 2H), 7.33–7.28 (m, 2H), 7.21 (dd, *J* = 8.6, 0.4 Hz, 1H), 6.85–6.80 (m, 2H), 6.79–6.75 (m, 1H), 6.72–6.67 (m, 1H), 6.53 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.78 (s, 1H), 4.92 (br s, 1H), 3.86 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.9, 142.5, 137.5, 135.3, 128.7 (2C), 127.9, 127.3, 127.3 (2C), 125.3, 124.5, 122.1, 121.2, 118.9, 116.8, 113.1, 112.7, 111.3, 109.5, 55.5, 55.4 ppm.

IR (neat): ν = 3416, 3061, 2245, 1599, 1506, 1452, 1219, 905, 727 cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{19}ON_2BrNa^+$ = [M+Na$^+$]: *m*/*z* = 429.0570, found: *m*/*z* = 429.0553.

2-Methoxy-*N*-[(5-nitro-1H-indol-2-yl)-phenyl-methyl]aniline (117)



117 was prepared according to *general procedure IV* using 5-nitroindole (32.4 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and benzaldehyde (42.4 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 39 h. 117 was purified by PTLC on silica gel (EtOAc/PE = 20:90; *eluted twice*).

Pale yellow solid.

Yield: 55.0 mg (74%).

Mp: 139–140 °C

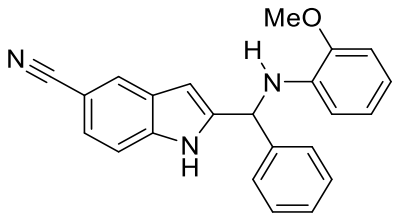
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 2.2 Hz, 1H), 8.43 (br s, 1H), 8.10 (dd, *J* = 9.0, 2.1 Hz, 1H), 7.50–7.45 (m, 2H), 7.39–7.33 (m, 3H), 7.31–7.27 (m, 1H), 7.07–7.04 (m, 1H), 6.83–6.78 (m, 1H), 6.77–6.72 (m, 1H), 6.71–6.66 (m, 1H), 6.51 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.84 (s, 1H), 4.90 (s, 1H), 3.83 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.9, 142.1, 141.9, 139.7, 137.2, 128.8 (2C), 127.6, 127.3 (2C), 126.2, 125.5, 121.6, 121.2, 118.1, 117.1, 116.9, 111.3, 111.3, 109.5, 55.6, 55.5 ppm.

IR (neat): ν = 3381.2, 2916, 2849, 1601, 1508, 1329, 1221, 1026, 733 cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{19}O_3N_3Na^+$ = [M+Na$^+$]: *m*/*z* = 396.1319, found: *m*/*z* = 396.1330.

2-[(2-methoxyanilino)-phenyl-methyl]-1H-indole-5-carbonitrile (114)



114 was prepared according to *general procedure IV* using 5-cyanoindole (28.4 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and benzaldehyde (42.9 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90

mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 114 was purified by PTLC on silica gel (EtOAc/PE = 1:9; *eluted twice*).

Colourless solid

Yield: 62.5 mg (89%).

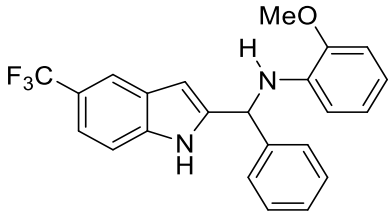
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.44 (br s, 1H), 7.94–7.88 (m, 1H), 7.48–7.42 (m, 2H), 7.42–7.37 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.30–7.26 (m, 1H), 6.98 (dd, *J* = 2.4, 0.8 Hz,1H), 6.80 (dd, *J* = 7.9, 1.4 Hz,1H), 6.77–6.72 (m, 1H), 6.68 (td, *J* = 7.7, 1.7 Hz, 1H), 6.50 (dd, *J* = 7.7, 1.5 Hz, 1H), 5.78 (d, *J* = 4.7 Hz, 1H), 4.87 (d, *J* = 4.8 Hz, 1H), 3.82 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 146.8, 142.1, 138.4, 137.2, 128.8 (2C), 127.6, 127.3 (2C), 125.9, 125.4, 125.3, 125.3, 121.2, 120.6, 120.1, 117.1, 112.1, 111.2, 109.5, 103.0, 55.6, 55.5 ppm.

IR (neat)**:** ν = 3331, 2916, 2849, 2220, 1514, 1275, 1227, 908, 731 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{19}ON_3Na^+$ = [M+Na^+]: *m*/*z* = 376.1420, found: *m*/*z* = 376.1422.

2-Methoxy-*N*-[(5-trifluoromethyl-1H-indol-2-yl)-phenyl-methyl]aniline (<u>112</u>)



112 was prepared according to *general procedure IV* using 5-trifluoromethylindole (37.0 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and benzaldehyde (42.4 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 43 h. 112 was purified by PTLC on silica gel (EtOAc/PE = 1:5; *eluted thrice*).

Colourless oil.

Yield: 64.8 mg (82%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.19 (br s, 1H), 7.87 (s, 1H), 7.52–7.46 (m, 2H), 7.44–7.41 (m, 2H), 7.38–7.33 (m, 2H), 7.31–7.26 (m, 1H), 6.93 (dd, *J* = 2.4, 0.9 Hz, 1H), 6.80 (dd, *J* = 7.9, 1.3 Hz, 1H), 6.74 (ap. td, *J* = 7.6, 1.4 Hz, 1H), 6.67 (ap. td, *J* = 7.6, 1.6 Hz, 1H), 6.51 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.82 (s, 1H), 4.93 (br s, 1H), 3.82 (s, 3H) ppm.

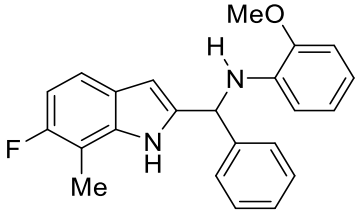
^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.9, 142.4, 138.0, 137.4, 128.7 (2C), 127.4, 127.3 (2C), 125.6 (q, *J* = 271.8 Hz), 125.5, 125.0, 122.1 (q, *J* = 31.9 Hz, 2C), 121.1, 120.2, 119.1 (q, *J* = 3.3 Hz), 117.3 (q, *J* = 4.0 Hz), 116.9, 111.5, 111.3, 109.4, 55.6, 55.4 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -60.29 ppm

IR (neat): ν = 3408, 2916, 2849, 1601, 1508, 1326, 1221, 1113, 736.8 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{19}FN_2O^+$ = [M+Na^+]: *m*/*z* = 395.1366, found: *m*/*z* = 395.1352.

2-Methoxy-*N*-[(7-methyl-6-fluoro-1H-indol-2-yl)-phenyl-methyl]aniline (<u>118</u>)



118 was prepared according to *general procedure IV* using 6-fluoro-7-methylindole (29.8 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and benzaldehyde (42.4 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 118 was purified by PTLC on silica gel (EtOAc/PE = 1:5; *eluted twice*).

Pale tan solid.

Yield: 63.7 mg (88%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (br s, 1H), 7.49–7.45 (m, 2H), 7.35–7.29 (m, 3H), 7.27–7.24 (m, 1H), 6.84–6.07 (m, 4H), 6.65 (td, *J* = 7.7, 1.6 Hz, 1H), 6.50 (dd, *J* = 7.9, 1.5 Hz, 1H), 5.76 (s, 1H), 4.90 (br s, 1H), 3.80 (s, 3H), 2.35 (s, 3H) ppm.

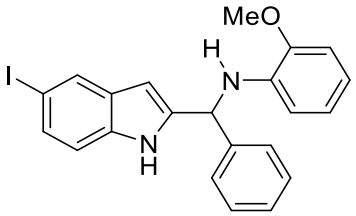
^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.7 (d, *J* = 236.4 Hz), 146.7, 142.7, 137.6, 136.7 (d, *J* = 9.5 Hz), 128.5, 127.3, 127.1, 123.2 (d, *J* = 3.0 Hz), 122.1, 119.8, 118.5, 117.4 (d, *J* = 10.0 Hz), 116.5, 115.0, 111.1, 110.5, 109.3, 108.6 (d, *J* = 25.4 Hz), 106.4 (d, *J* = 21.9 Hz), 55.6, 55.4, 8.8 (d, *J* = 4.5 Hz) ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –62.50 ppm.

IR (neat): ν = 3418, 2916, 2849, 1601, 1504, 1221, 907, 729 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{21}ON_2FNa^+$ = [M+Na^+]: *m*/*z* = 383.1527, found: *m*/*z* = 383.1526.

2-Methoxy-*N*-[(5-iodo-1H-indol-2-yl)-phenyl-methyl]aniline (111)



111 was prepared according to *general procedure IV* using 5-iodoindole (48.6 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and benzaldehyde (42.5 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 111 was purified by PTLC on silica gel ($EtOAc/NEt_3$/PE = 9:1:90; *eluted thrice*)

Brown solid

Yield: 64.4 mg (71%).

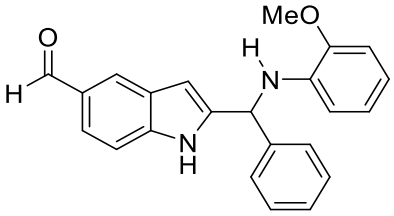
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (br s, 1H), 7.97–7.94 (m, 1H), 7.50–7.46 (m, 3H), 7.39–7.35 (m, 2H), 7.33–7.30 (m, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.84 (dd, J = 7.8, 1.4 Hz, 1H), 6.80–6.75 (m, 2H), 6.74–6.68 (m, 1H), 6.53 (dd, *J* = 7.8, 1.5 Hz, 1H), 5.78 (d, *J* = 4.2 Hz, 1H), 4.93 (d, *J* = 4.3 Hz, 1H), 3.87 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.9, 142.5, 137.5, 135.7, 130.8, 128.7, 128.6 (2C), 128.3, 127.3 (2C), 127.3, 124.1, 121.2, 118.6, 116.8, 113.2, 111.3, 109.5, 83.4, 55.5 ppm.

IR (neat): ν = 3416, 2928, 2245, 1506, 1221, 1026, 905, 726 cm^{-1}.

HRMS (ESI): calculated for $C_{22}H_{19}ON_2INa^+$ = [M+Na^+]: *m*/*z* = 477.0434, found: *m*/*z* = 477.0438.

2-Methoxy-*N*-[(5-formyl-1H-indol-2-yl)-phenyl-methyl]aniline (115)



115 was prepared according to *general procedure IV* using 5-formylindole (29.0 mg, 0.20 mmol, 1.00 equiv), *o*-anisidine (49.3 mg, 0.40 mmol, 2.00 equiv) and benzaldehyde (42.4 mg, 0.40 mmol, 2.00 equiv), in the presence of Li_2CO_3 (1.50 mg, 0.01 mmol, 5 mol%), CuCl (1.90 mg, 0.01 mmol, 5 mol%), $NaBF_4$ (2.20 mg, 0.01 mmol, 5 mol%) as the catalyst components, in 2-MeTHF (200 µL, 1 M), at 30 °C for 15 h. 115 was purified by PTLC on silica gel (EtOAc/ PE =10:90; *eluted thrice*)

Colourless solid.

Yield: 61.2 mg (86%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.99 (s, 1H), 8.42–8.29 (m, 1H), 8.24–8.08 (m, 1H), 7.81 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.55–7.50 (m, 2H), 7.47 (dt, *J* = 8.5, 0.7 Hz, 1H), 7.41–7.35 (m, 2H), 7.32 (d, *J* = 7.3 Hz, 1H), 6.99 (dd, *J* = 2.5, 1.0 Hz, 1H), 6.83 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.78 (td, *J* = 7.6, 1.4 Hz, 1H), 6.70 (td, *J* = 7.7, 1.6 Hz, 1H), 6.55 (dd, *J* = 7.8, 1.6 Hz, 1H), 5.90 (s, 1H), 4.97 (s, 1H), 3.85 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 192.4, 146.8, 142.3, 140.1, 137.3, 129.7, 128.7 (2C), 127.4, 127.3 (2C), 126.1, 125.3, 124.9, 122.4, 121.2, 121.1, 116.9, 111.9, 111.2, 109.4, 55.5, 55.4 ppm.

IR (neat): ν = 3383, 2916, 2359, 1670, 1508, 1175, 733 cm^{-1}.

HRMS (ESI): calculated for $C_{23}H_{20}N_2O_2Na^+$ = [M+Na^+]: *m*/*z* = 379.1417, found: *m*/*z* = 379.1420.

3.3 Conjugate addition with CDP

3.3.1 General Procedures

Solvent screening – conjugate addition (general procedure I)

In a nitrogen glove box, a dry screw-capped vial with a magnetic stirrer bar was charged with CDP (2.10 mg, 4.00 μmol, 1.00 mol%), Michael acceptor (39.6 mg, 400 μmol, 1.00 equiv), solvent (750 μL) and MeCN (45.0 μL, 2.00 equiv). The reaction mixture was stirred at 40 °C for 3 h. The internal standard, dibenzyl ether, was added prior to ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture.

Base screening – conjugate addition (general procedure II)

In a nitrogen glove box, a dry screw-capped vial with a magnetic stirrer bar was charged with base (4.00 μmol, 1 mol%), dimethylacrylamide (39.6 mg, 400 μmmol, 1.00 equiv), MeCN (800 μL). The reaction mixture was stirred at 40 °C for 3 h. The internal standard, dibenzyl ether, was added prior to ^{1}H NMR spectroscopic analysis of an aliquot of the reaction mixture.

Alkyl carbene control experiments – conjugate addition (general procedure III)

In a nitrogen glove box, a dry screw-capped vial with a magnetic stirrer bar was charged with KHMDS (1.60 mg, 8.00 μmol, 1.00 mol%), carbene salt (12.0 μmol, 1.20 mol%) and MeCN (400 μL) and stirred at 40 °C for 24 h. Dimethylacrylamide (39.6 mg, 400 μmol, 1.00 equiv), and MeCN (400 μL) were added and the solution stirred at 40 °C for 3 h. The internal standard, dibenzyl ether, was added prior to ^{1}H NMR analysis of an aliquot of the reaction mixture.

Aryl carbene control experiments – conjugate addition (general procedure IV)

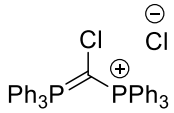
In a nitrogen glove box, a dry screw-capped vial with a magnetic stirrer bar was charged with KHMDS (1.60 mg, 8.00 μmol, 1.00 mol%), carbene salt (12.0 μmol, 1.20 mol%) and MeCN (400 μL) and stirred at 40 °C for 1 h. Dimethylacrylamide (39.6 mg, 400 μmol, 1.00 equiv), and MeCN (400 μL) were added and the solution stirred at 40 °C for 3 h. The internal standard, dibenzyl ether, was added prior to ^{1}H NMR analysis of an aliquot of the reaction mixture.

Substrate screen – conjugate addition (general procedure V)

In a nitrogen glove box, a dry screw-capped vial with a magnetic stirrer bar was charged with CDP (2.20 mg, 5.00 μmol, 10.0 mol%), amide (100 or 50 μmol, 1.00 equiv), and alkyl nitrile (100-200 μL). The reaction mixture was stirred at the specified temperature for the specified time. The internal standard, dibenzyl ether, was added prior to ^{1}H NMR analysis of an aliquot of the reaction mixture. For reactions which gave no reaction the mixture was heated to 80 °C for 63 h and ^{1}H NMR analysis repeated.

3.3.1 Preparation of catalysts

1-Chloro-methylenebis(triphenylphosphonium) chloride (<u>158</u>)[141]



To a solution of triphenylphosphine (26.2 g, 100 mmol, 1.50 equiv) in DCM (50 mL) tetrachloromethane (6.43 mL, 66.7 mmol) was added dropwise at room temperature. The mixture was stirred for 26 h upon which the solution changed colour from yellow to brown and a white precipitate formed. 1,2-epoxybutane (5.80 mL, 66.7 mmol, 1.00 equiv) was added while ensuring that the temperature did not rise above 20 °C. The white precipitate dissolved and ether (50 mL) was added dropwise until a precipitate formed. The product was crystallised at 0 °C and was then filtered, washed with DCM (2 x 2 mL) and Et_2O (2 x 2 mL) and recrystallised from DCM and Et_2O.

Colourless solid

Yield: 12.4 g (31%).

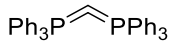
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.61 (m, 6H), 7.61–7.53 (m, 12H), 7.53–7.43 (m, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 134.0 (6C), 133.8 (t, *J* = 5.0 Hz, 12C), 129.7 (t, *J* = 6.2 Hz, 12C), 123.2 (d, *J* = 94.3 Hz, 6C), 123.1 (dd, *J* = 76.0, 74.5 Hz) ppm.

^{31}P NMR (220 MHz, $CDCl_3$): δ = 25.8 ppm.

IR (neat)**:** ν = 3096, 1663, 1491, 1406, 1261, 993, 766, 697 cm^{-1}.

Hexaphenylcarbodiphosphorane (<u>153</u>)[142]



In a nitrogen filled glovebox 1-chloro-methylenebis(triphenylphosphonium) chloride (1.60 g, 2.64 mmol, 1.00 equiv) was suspended in benzene (6 mL) and tris(dimethylamino) phosphine (0.43 g, 2.64 mmol, 1.00 equiv) added. The mixture was stirred for 24 h at 25 °C. The solution was heated and held at reflux for 5 min before being filtered through a G4 sintered frit. The hot solution was cooled slowly and crystallised spontaneously. The crystals were filtered and washed with benzene (1 mL). After a second recrystallization from benzene the crystals were crushed and dried *in vacuo*. The compound was stored in a nitrogen glovebox.

Yellow solid

Yield: 1.05 g (75%).

Mp: 214 – 215 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.89–7.85 (m, 12H), 7.08–6.95 (m, 18H) ppm.

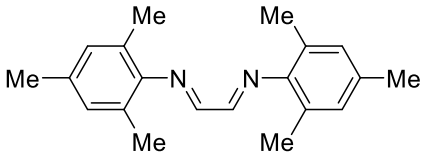
^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.9 (pent, *J* = 48.3 Hz), 132.3 (t, *J* = 5.4 Hz, 6C), 129.1 (12C), 128.3 (12C), 128.1 (6C) ppm.

^{31}P NMR (220 MHz, $CDCl_3$): δ = –4.1 ppm.

IR (neat)**:** ν = 1464, 1431, 1094, 752, 691 cm^{-1}.

HRMS (EI): calculated for $C_{37}H_{30}P_2^+$ = [M^+]: *m*/*z* = 536.1739, found: *m*/*z* = 536.1739.

N,*N*'-bis(2,4,6-trimethylphenyl)ethanediimine (328) [229]



To an oven dried flask was added 1,3,5-trimethylaniline (31.9 mL, 169 mmol, 2.00 equiv) methanol (85 mL) and the solution was stirred for 5 min. Glyoxal (9.7 mL, 84.6 mmol, 40% in water, 1.00 equiv) was added followed by formic acid (0.2 ml). After 10 min a yellow solid precipitated. Additional methanol was added (85 mL) to facilitate stirring. The mixture was left stirring for 24 hours at room temperature. The suspension was filtered under vacuum and the precipitate was washed with methanol (3 x 20 mL). The volatiles were removed *in vacuo* to afford product **328**.

Yellow solid

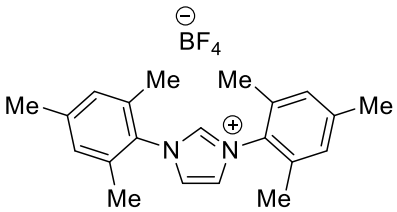
Yield: 23.5 g (76%).

Melting point: 214–215 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.31 (s, 2H), 6.94 (s, 4H), 2.23 (s, 6H), 2.19 (s, 12H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.5 (4C), 147.4 (2C), 134.2 (2C), 129.0 (4C), 126.5 (2C), 20.8 (2C), 18.2 (4C) ppm.

2,6-bis(mesityl)imidazolium chloride (176-BF_4)[230]



Under an atmosphere of argon *N*,*N*'-bis(2,4,6-trimethylphenyl)ethanediimine (17.2 g, 58.5 mmol, 1.00 equiv), was dissolved in ethyl acetate (120 mL). Paraformaldehyde (1.92 g, 64.0 mmol, 1.10 equiv), and HCl (4 M in dioxane, 177 mmol, 3.00 equiv) were added and stirred at 25 °C for 20 h. The colourless precipitate was filtered and the ethyl acetate solution was dried to an amorphous solid and recrystallized with chloroform. This solid (9.60 g) was dissolved in

water (170 ml) and tetrafluroboric acid (4.04 mL, 28.2 mmol, 1.1 equiv) was added. Extraction with DCM (200 mL) drying over magnesium sulfate and drying *in vacuo* afforded a pale brown solid. This solid was dissolved in the minimum amount of DCM and precipitated with Et_2O. After filtration the product was dried *in vacuo.*

Yield: 6.9 g (68%)

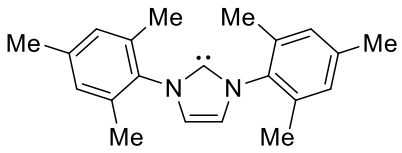
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.92 (s, 1H), 7.58 (s, 2H), 7.07 (s, 4H), 2.38 (s, 6H), 2.15 (s, 12H) ppm.

^{13}C NMR (500 MHz, $CDCl_3$): δ = 138.9, 137.0 (2C), 135.2 (4C), 128.9 (4C), 128.0 (2C), 120.3 (2C), 20.7 (2C), 17.8 (4C) ppm.

^{11}B NMR (160 MHz, $CDCl_3$): δ = -1.25 ppm.

^{19}F NMR (160 MHz, $CDCl_3$): δ = -152.60 ppm.

[1,3-bis(2,4,6-trimethylphenyl)imidazol]-2-ylidene(176)[230]



Under an atmosphere of argon 1,3-bis(mesityl)imidazolium chloride (2.00 g, 5.00 mmol, 1.00 equiv) was dissolved in THF (20 mL) and sodium hydride (240 mg, 10.0 mmol, 2.00 equiv) added followed by a catalytic quantity of KO^{t}Bu (~20 mg). The mixture was stirred for 15 h filtered through a G4 sintered frit and concentrated to half the original volume. Pentane (10 mL) was precipitating a colourless solid which was collected by suction filtration. The solid was dried *in vacuo* and stored under argon at -20 ^{o}C.

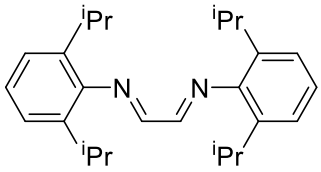
Yield: 1.25 g (82%)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.81 (s, 4H), 6.48 (s, 2H), 2.16 (s, 18H) ppm.

^{13}C NMR (500 MHz, $CDCl_3$): δ = 138.9, 137.0 (2C), 135.2 (4C), 128.9 (2C), 120.3 (4C), 20.7 (2C), 17.8 (6C) ppm.

HRMS (EI): calculated for $C_{21}H_{23}N_2^+$ = [M^+]: *m*/*z* = 303.1856, found: *m*/*z* = 303.1858

N,*N*'-bis(2,6-diisopropylphenyl)ethanediimine (329)



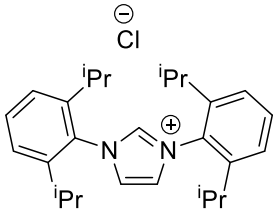
To a solution of 2, 6 diisopropylaniline (7.09 g, 40.0 mmol, 2.00 equiv) in methanol (50 ml) was added glyoxal (20 mmol, 40% aq), 1.00 equiv). Formic acid (3 drops) was added and the solution stirred for 5 h. The bright yellow precipitate formed was filtered and washed with methanol (3 x 50 ml) and dried *in vacuo* to constant weight.

Yield: 6.80 g (90%)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.13 (s, 2H), 7.24–7.17 (m, 6H), 2.97 (sept, *J* = 6.9 Hz, 4H), 1.24 (d, *J* = 6.9 Hz, 24H) ppm.

^{13}C NMR (500 MHz, $CDCl_3$): δ = 163.1 (2C), 148.0 (2C), 136.7 (4C), 125.1 (2C), 123.2 (4C), 28.1 (4C), 23.4 (8C) ppm.

2,6-bis(diisopropylphenyl)imidazolium chloride (177-Cl)



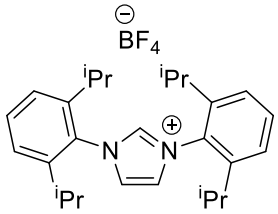
To a stirred solution of 329 (6.8 g, 18.0 mmol, 1 equiv) in ethyl acetate (160 ml) was added paraformaldehyde (560 mg, 18.7 mmol, 1.04 equiv) followed by trimethylsilyl chloride (2.4 ml, 19 mmol, 1.05 equiv) under an argon atmosphere. The solution was heated to 70 ^{o}C and maintained at this temperature for 3 h. The mixture was cooled to ambient whereupon the product crystallises from solution. The solid was filtered and washed with ethyl acetate (3 x 100 ml) and dried *in vacuo*.

Yield: 6.60 g (87%)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.14 (s, 1H), 8.15 (s, 2H), 7.59 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 4H), 2.47 (sept, *J* = 6.8 Hz, 4H), 1.31 (d, *J* = 6.8 Hz, 12H), 1.26 (d, *J* = 6.8 Hz, 12H) ppm.

^{13}C NMR (500 MHz, $CDCl_3$): δ = 163.1 (2C), 148.0 (2C), 136.7 (4C), 125.1 (2C), 123.2 (4C), 28.1 (4C), 23.4 (8C) ppm.

2,6-bis(diisopropylphenyl)imidazolium tetrafluoroborate (177-BF_4)



To a stirred solution of 177-Cl (6.60 g, 17.00 mmol, 1 equiv) in water (250 ml) was added HBF_4 (4.30 g, 18.7 mmol, 1.10 equiv, 38% aq) and the mixture was stirred at ambient for 30 minutes. DCM (50 ml) was added and the organic layer separated. Diethyl ether (~50 ml) was added to precipitate a colourless solid which was filtered under vacuum and washed with diethyl ether (2 x 20 ml). The colourless solid was dried under *in vacuo*.

Yield: 6.60 g (87%)

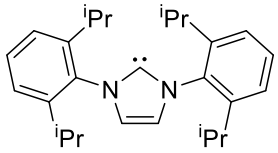
^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.14 (s, 1H), 8.15 (s, 2H), 7.59 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 4H), 2.47 (sept, *J* = 6.8 Hz, 4H), 1.31 (d, *J* = 6.8 Hz, 12H), 1.26 (d, *J* = 6.8 Hz, 12H) ppm.

^{13}C NMR (500 MHz, $CDCl_3$): δ = 163.1 (2C), 148.0 (2C), 136.7 (4C), 125.1 (2C), 123.2 (4C), 28.1 (4C), 23.4 (8C) ppm.

^{11}B NMR (160 MHz, $CDCl_3$): δ = -1.25 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -152.6 ppm

[1,3-bis(2,6-diisopropylphenyl)imidazol]-2-ylidene (177)[230]



Under an atmosphere of argon 1,3-bis(diisopropyl)imidazolium chloride (2.55 g, 5.00 mmol, 1.00 equiv) was dissolved in THF (20 mL) and sodium hydride (240 mg, 10.0 mmol, 2.00 equiv) added followed by a catalytic quantity of KO^{t}Bu (~20 mg). The mixture was stirred for 15 h filtered through a G4 sintered frit and concentrated to half the original volume. Pentane (10 mL) was precipitating a colourless solid which was collected by suction filtration. The solid was dried *in vacuo* and stored under argon at -20 ^{o}C.

Yield: 1.41 g (73%)

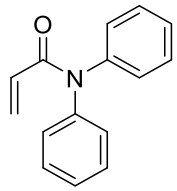
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29 (t, *J* = 7.3 Hz, 2H), 7.18 (d, *J* = 7.3 Hz, 4H), 6.62 (s, 2H), 2.96 (sept, *J* = 6.9 Hz, 4H), 1.28 (d, *J* = 6.9 Hz, 12H), 1.19 (d, *J* = 6.9 Hz, 12H) ppm.

^{13}C NMR (500 MHz, $CDCl_3$): δ = 146.0 (4C), 138.7, 128.8 (2C), 128.1 (2C), 123. 4 (4C), 121.3 (2C), 28.5 (4C), 24.5 (4C), 23.3 (4C) ppm.

HRMS (EI): calculated for $C_{27}H_{36}N_2^+ = [M^+]$: *m*/*z* = 388.2873, found: *m*/*z* = 388.2853.

3.3.2 Unsubstituted amide starting materials

N, N Diphenylacrylamide (330)[231]



To a solution of acryloyl chloride (2.00 g, 22.1 mmol, 1.00 equiv) in DCM (20 mL) was added diphenylamine (3.40 g, 22.1 mmol, 1.00 equiv) dissolved in DCM (10 mL) cautiously. The brown solution was stirred for 14 h and water (20 ml) added. The organic layer was separated and the aqueous washed with DCM (2 x 25 ml) and dried over magnesium sulfate. Removal of the solvent in vacuo afforded a tar which was refluxed in methanol (10 ml) and cooled to -20 °C whereupon the titled compound crystalised as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 650 mg (15%).

Mp: 78–79 °C

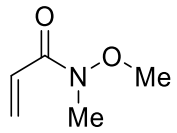
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.32 (m, 4H), 7.28–7.14 (m, 6H), 6.47 (dd, *J* = 16.8, 1.9 Hz, 1H), 6.19 (dd, *J* = 16.8, 10.3 Hz, 1H), 5.62 (dd, *J* = 10.3, 1.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 142.5 (2C), 129.6 (4C), 129.3 (2C), 128.5, 128.4 (4C), 126.9 ppm.

IR (neat)**:** ν = 3096, 1663, 1491, 1406, 1261, 993, 766, 697 cm^{-1}.

HRMS (EI): calculated for $C_{15}H_{13}ON^{+}$ = [M^{+}]: *m*/*z* = 223.0992, found: *m*/*z* = 223.0991.

***N*-methoxy-*N*-methylacrylamide (331)[232]**



To a stirred solution of acryloyl chloride (2.00 ml, 24.8 mmol, 1.00 equiv) in DCM (20 ml) at ambient temperature under an argon atmosphere was added *N*, *O*-dimethylhydroxylamine hydrochloride (2.90 g, 29.8 mmol, 1.20 equiv) and sodium bicarbonate (5.20 g, 62.0 mmol, 2.50 equiv) and the suspension stirred for 3 h. To the solution was added HCl (20 ml, 1M) and the organic layer separated and washed with sodium bicarbonate (3 x 10 ml, sat. aq.) followed by brine (20 ml). The combined

organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Distillation under reduced pressure afforded **331** as a colourless solution, which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless liquid

Yield: 2.10 g (74%).

Bp: 62–64 °C (20 mbar)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.73 (dd, *J* = 17.1, 10.4 Hz, 1H), 6.43 (dd, *J* = 17.1, 2.0 Hz, 1H), 5.75 (dd, *J* = 10.4, 2.0 Hz, 1H), 3.71 (s, 3H), 3.26 (s, 3H) ppm.

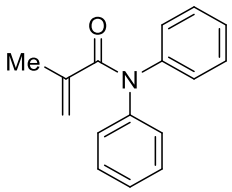
^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 129.0, 126.0, 61.8, 32.3 ppm.

IR (neat)**:** ν = 2968, 2940, 1655, 1620, 1419, 1179, 995, 787 cm^{-1}.

HRMS (EI): calculated for $C_5H_9O_2N^+ = [M^+]$: *m*/*z* = 115.0627, found: *m*/*z* = 115.0612.

3.3.3 α-substituted Michael amides

_N_,_N_-diphenylacrylamide (332)[233]



To a solution of methacryloyl chloride (1.61 g, 15.0 mmol, 1.50 equiv), diphenylamine (1.69 g, 10.0 mmol , 1.00 equiv) in toluene (15 ml). The crude was recrystalised using diethyl ether yielding a colourless solid which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Colourless solid.

Yield: 1.60 mg (50%).

Mp: 102–103 °C (Lit.: 102–103 °C).[234]

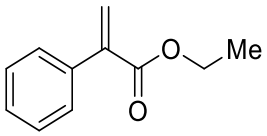
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 4H), 7.25–7.19 (m, 2H), 7.19–7.12 (m, 4H), 5.23 (s, 1H), 5.17 (s, 1H), 1.84 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.86, 143.52, 141.22, 129.1 (4C), 127.2 (4C), 126.5 (2C), 120.9 (2C), 19.9 ppm.

IR (neat)**:** ν = 3067, 2945, 1655, 1589, 1489, 1339, 1229, 945, 71 cm^{-1}.

HRMS (EI): calculated for $C_{16}H_{15}NO^+$ = [M^+]: *m*/*z* = 237.1148, found: *m*/*z* =237.1158.

2-Phenylacrylic acid ethyl ester (333)[235]



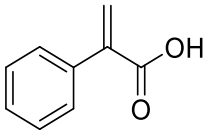
To a solution of ethyl phenylacetate (3.20 ml, 20.0 mmol, 1.00 equiv) in DMF (90 ml) was added potassium carbonate (2.80 g, 20.0 mmol, 1.00 equiv) and formaldehyde (2.30 ml, 28.4 mmol, 1.42 equiv, 37% aq) and the solution heated to 110 °C for 3 h. The solution was cooled to ambient and water (200 ml) was added and the solution extracted with diethylether (3 x 100 ml). The combined organic fractions were washed with HCl (3 x 100 ml, 6M) and dried over magnesium sulfate and the solvent dried *in vacuo* yielding a pale yellow solid which was used without further purification.

Yellow solid

Yield: 1.84 g (54%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46–7.42 (m, 2H), 7.39–7.34 (m, 3H), 6.37 (d, *J* = 1.3 Hz, 1H), 5.91 (d, *J* = 1.3 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H) ppm.

2-Phenylacrylic acid (334)[236]



2-Formyl ethyl phenylacetate (1.76 g, 10.0 mmol, 1.00 equiv) was refluxed in in lye (20 ml, 1 M aq) for 13 h. The solution was washed with diethylether (2 x 20 ml) and acidified with HCl (20 ml, 3M aq). The aqueous solution was extracted with diethylether (2 x 40 ml) dried over magnesium sulfate and the solvent removed *in vacuo* affording the titled compound.

Waxy colourless solid.

Yield: 800 mg (56%).

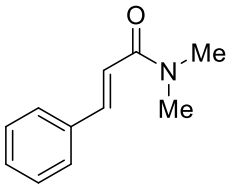
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.50–7.43 (m, 2H), 7.42–7.35 (m, 3H), 6.57 (s, 1H), 6.05 (s, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 140.5, 136.1, 129.3, 128.4 (2C), 128.4, 128.2 (2C) ppm.

IR (neat)**:** ν = 2940, 2617, 1684, 1429, 1217, 899, 701 cm^{-1}.

3.3.4 β-substitued Michael amides

(*E*)-*N*, *N*-Dimethyl-3-phenylacrylamide (355)[237]



To a stirred solution of *trans*-cinnamic acid (1.48 g, 10.0 mmol, 1.00 equiv) in DCM (25 ml) at ambient temperature under an argon atmosphere was added thionyl chloride (2.38 g, 20.0 mmol, 2.00 equiv) and the solution stirred for 4 h. The solvent and excess thionyl chloride was removed *in vacuo* affording a colourless solid which was dissolved in toluene (20 ml). Dimethylammonium chloride (735 mg, 9.00 mmol, 0.90) was added followed by pyridine (1.57 g, 20.0 mmol, 2.00 equiv) and the reaction stirred for 15 h. Water (20 ml) was added and the mixture was extracted with DCM (3 x 20 ml) and washed with $NaHCO_3$ (20 ml, sat. aq.). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystallisation from methanol afforded **355** as a colourless solid, which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Colourless solid

Yield: 1.25 g (71%).

Mp: 94–95 °C (Lit.: 94–96 °C).[238]

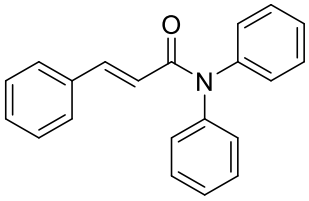
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 15.4 Hz, 1H), 7.53 (d, *J* = 7.3 Hz, 2H), 7.43–7.30 (m, 3H), 6.89 (d, *J* = 15.4 Hz, 1H), 3.17 (s, 3H), 3.07 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 142.3, 135.4, 129.5, 128.8 (2C), 127.8 (2C), 117.5, 37.4, 35.9 ppm.

IR (neat)**:** ν = 3078, 2930, 2359, 1651, 1599, 1396, 1140, 995, 767 cm^{-1}.

HRMS (EI): calculated for $C_{11}H_{13}ON^+$ = [M^+]: *m*/*z* = 175.0992, found: *m*/*z* = 175.0997.

N,N-Diphenyl-3-phenyl-2-propenamide (336)[239]



To a solution of cinamoyl chloride (1.12 g, 6.70 mmol, 1.00 equiv) in DCM (10 ml) was added diphenylamine (1.14 g, 6.70 mmol, 1.00 equiv) portion wise with stirring. The reaction was

bought to reflux and maintained for 4 h. Water (10 ml) was added and the biphasic mixture extracted with ethyl acetate (3 x 10 ml). The combined organic fractions were dried over $MgSO_4$ and the solvent removed under reduced pressure affording the crude product. Recrystallisation from *iso*propanol afforded the titled compound as colourless prismatic crystals which were dried over molecular sieves in diethylether. Ether was removed under reduced pressure and the solid ground and further dried *in vacuo* before use.

Colourless solid

Yield: 1.38 g, (69%).

Melting point: 153–154 °C

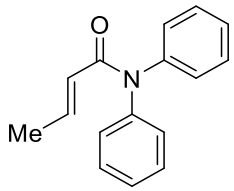
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 15.5 Hz, 1H), 7.43–7.37 (m, 6H), 7.32–7.28 (m, 9H), 6.51 (d, *J* = 15.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 142.8, 142.6 (2C), 135.1, 129.7, 129.3 (4C), 128.8 (2C), 128.0 (2C), 126.9 (br, 6C), 119.8 ppm.

IR (neat): 3662, 3005, 2937, 2864, 1658, 1487, 1448, 1352, 1255, 761, 569 cm^{-1}

HRMS (EI): calculated for $C_{21}H_{17}O_1N^+$ = $[M^+]$: *m*/*z* = 299.1301, found: *m*/*z* = 299.1304.

(*E*)-*N*, *N*-diphenyl-2-butenamide (<u>337</u>)[240]



To a stirred solution of *trans*-crotonic acid (3.44 g, 40.0 mmol, 1.00 equiv) in DCM (30 ml) at ambient temperature under an argon atmosphere was added thionyl chloride (4.76 g, 40.0 mmol, 1.00 equiv) and the solution stirred for 15 h. Diphenyl amide (6.09 g, 36.0 mmol, 0.90 equiv) was added followed by triethylamine (5.02 ml, 36.0 mmol, 0.90 equiv) dropwise and the mixture stirred for an additional 6 h. The solution was washed with K_2CO_3 (3 x 20 ml sat. aq.) followed by brine (20 ml). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo.* Recrystalisation from ethanol afforded **292** as tan prismatic crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Tan solid

Yield: 1.70 g (18%).

Mp: 110–111 °C

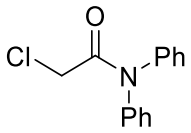
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.31 (m, 4H), 7.28–7.20 (m, 6H), 7.03 (dq, *J* = 15.1, 6.9 Hz, 1H), 5.87 (dq, *J* = 15.1, 1.7 Hz, 1H), 1.79 (dd, *J* = 6.9, 1.7 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 142.9 (2C), 142.4 (4C), 129.2 (2C), 127.7, 126.7, 123.9 (4C), 18.1 ppm.

IR (neat)**:** ν = 3059, 2357, 1665, 1489, 1344, 1251, 637 cm^{-1}.

HRMS (EI): calculated for $C_{16}H_{15}ON^{+}$ = [M^{+}]: *m*/*z* = 237.1148, found: *m*/*z* = 237.1147.

2-Chloro-*N*,*N*-diphenylacetamide (338)[241]



To a stirred solution of chloroacetylchloride (16.9 g, 150 mmol, 1.00 equiv) in toluene (200 ml) at ambient temperature under an argon atmosphere was added diphenylamine (25.4 g, 150 mmol, 1.00 equiv). The mixture was heated at 90 °C for 14 h after which the solvent was removed in vacuo. The oil formed was purified by column chromatography eluting DCM affording a pale liquid which solidified on standing.

Colourless waxy solid

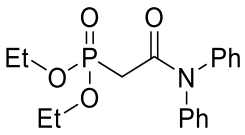
Yield: 24.5 g (67%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.38 (m, 4H), 7.38–7.20 (m, 6H), 4.05 (s, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 144.9 (2C), 129.2 (br 4C), 128.6 (br 4C), 126.1 (2C), 42.7 ppm.

IR (neat)**:** ν = 2945, 1676, 1491, 1362, 1263, 689 cm^{-1}.

***N*,*N*-Diphenyldiethylphosphonacetamide (339)[242]**



To a stirred solution of 338 (24.5 g, 100 mmol, 1.00 equiv) in DMF (160 ml) at ambient temperature under an argon atmosphere was added triethylphosphite (25.7 ml, 150 mmol, 1.50 equiv) and sodium iodide (1.50 g, 10.0 mmol, 0.10 equiv). The mixture was heated at 110 °C for 14 h and the solvent was removed *in vacuo*. The tar was dissolved in ethyl acetate (200 ml) and activated charcoal (~2 spatulas) was added and stirred for 10 minutes before filtering through celite. HCl (50 ml, 6M) was added and the organic layer separated and washed with additional HCl (2 x 50 ml, 6M). The organic layer was dried over magnesium sulfate and solvent removed *in vacuo* affording a colourless solid which solidified on standing.

Colourless waxy solid

Yield: 20.5 g (59%).

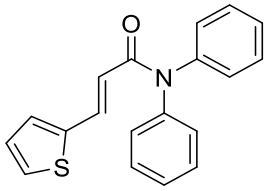
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.16 (m, 10H), 4.23–4.15 (m, 4H), 3.07 (s, 1H), 3.02 (s, 1H), 4.05 (s, 2H), 1.35 (t, *J* = 7.1 Hz, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2, 142.6 (d, *J* = 55.9 Hz), 129.9 (2C), 129.0 (2C), 128.8 (2C), 128.2, 126.6 (2C), 62.6 (d, *J* = 6.5 Hz, 2C), 34.4 (d, *J* = 136.6 Hz), 16.4 (d, *J* = 6.5 Hz, 2C) ppm.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 21.0 ppm

IR (neat)**:** ν = 2980, 2924, 1655, 1491, 1348, 1246, 1020, 962, 694 cm^{-1}.

Trans-*N*,*N*-diphenyl-3-(thiophen-2-yl) acrylamide (340)[243]



To a stirred solution of *trans*-2-thiopheneacrylic acid (1.54 g, 10.0 mmol, 1.00 equiv) in DCM (25 ml) at ambient temperature under an argon atmosphere was added thionyl chloride (2.38 g, 20.0 mmol, 2.00 equiv) and the solution stirred for 4 h. The solvent and excess thionyl chloride was removed *in vacuo* affording a tan solid which was dissolved in toluene (20 ml). Diphenylamine (1.69 g, 10.0 mmol, 1.00 equiv) was added followed by triethylamine (1.01 g, 10.0 mmol, 1.00 equiv) and the reaction stirred for 15 h. Water (20 ml) was added and the mixture was extracted with DCM (3 x 20 ml) and washed with brine (20 ml). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystallisation from methanol afforded **340** as a colourless solid, which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Colourless solid

Yield: 2.90 g (95%).

Mp: 158–160 °C

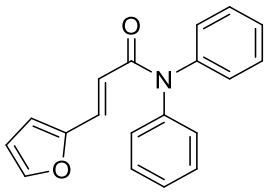
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 15.2 Hz, 1H), 7.45–7.33 (m, 4H), 7.32–7.21 (m, 7H), 7.16 (d, *J* = 3.5 Hz, 1H), 6.99 (dd, *J* = 4.9, 3.5 Hz, 1H), 6.27 (d, *J* = 15.2 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0, 142.8, 140.4, 135.2 (4C), 130.2 (4C), 129.3, 128.0 (2C), 127.7 (2C), 126.9, 118.8 (2C) ppm.

IR (neat)**:** ν = 3026, 1661, 1609, 1489, 1319, 1250, 995, 833, 754, 729 cm^{-1}.

HRMS (EI): calculated for $C_{19}H_{15}ON^{32}S^{+}$ = [M^{+}]: *m*/*z* = 305.0869, found: *m*/*z* = 305.0876.

***(E)-N,N*-diphenyl-3-(fur-2-yl) acrylamide (<u>341</u>)[243]**



To a stirred solution of *trans*-2-furylacrylic acid (1.38 g, 10.0 mmol, 1.00 equiv) in DCM (25 ml) at ambient temperature under an argon atmosphere was added thionyl chloride (2.38 g, 20.0 mmol, 2.00 equiv) and the solution stirred for 4 h. The solvent and excess thionyl chloride was removed *in vacuo* affording a tan solid which was dissolved in toluene (20 ml). Diphenylamine (1.69 g, 10.0 mmol, 1.00 equiv) was added followed by triethylamine (1.01 g, 10.0 mmol, 1.00 equiv) and the reaction stirred for 15 h. Water (20 ml) was added and the mixture was extracted with DCM (3 x 20 ml) and washed with brine (20 ml). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystallisation from methanol afforded **341** as a colourless solid, which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Colourless solid

Yield: 2.64 g (91%).

Mp: 179–180 °C (Lit.: 181.5 °C).

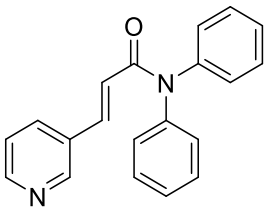
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 15.3 Hz, 1H), 7.45–7.32 (m, 5H), 7.31–7.19 (m, 6H), 6.53 (d, *J* = 3.3 Hz, 1H), 6.40 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.37 (d, *J* = 15.3 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 151.6, 144.2 (4C), 142.8, 129.4 (4C), 129.2, 126.8, 117.4 (2C), 114.2 (2C), 112.14 (2C) ppm.

IR (neat)**:** ν = 3111, 1655, 1609, 1487, 1350, 1267, 708, 615 cm^{-1}.

HRMS (EI): calculated for $C_{19}H_{15}O_2N^+ = [M^+]$: *m*/*z* = 289.1097, found: *m*/*z* = 289.1104.

***(E)-N,N*-diphenyl-3-(pyridine-3-yl)acrylamide (<u>342</u>)[244]**



To a stirred suspension of *trans*-3-(3-pyridyl)acrylic acid (1.00 g, 6.70 mmol, 1.00 equiv) in DCM (6 mL) at 0 °C under an argon atmosphere was added triethylamine (1.10 ml, 8.04 mmol, 1.20 equiv) followed by oxalyl chloride (1.78 g, 13.9 mmol, 2.00 equiv). After 1 h the solution

was warmed to ambient and stirred for 17 h. The solvent was removed *in vacuo* and the solid redissolved in DCM (20 ml). Diphenylamine (1.36 g, 8.04 mmol, 1.20 equiv) was added in 3 portions over 15 minutes and stirred at ambient for 6 h. The solvent was removed *in vacuo* and the crude solid purified by column chromatography eluting 10% EtOAc:Hexanes (rf = 0.1) yielding a pale yellow solid which was dried over molecular sieves (4 Å) in diethyl ether at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Pale yellow solid.

Yield: 750 mg (40%).

Mp: 131–132 °C.

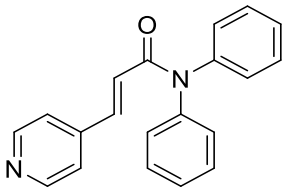
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.61 (d, *J* = 2.1 Hz, 1H), 8.53 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.74 (d, *J* = 15.6 Hz, 1H), 7.61 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.47–7.35 (m, 4H), 7.34–7.28 (m, 4H), 7.28–7.26 (m, 2H), 7.24 (dd, *J* = 8.0, 4.8, Hz, 1H), 6.55 (d, *J* = 15.6 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.5, 150.4, 149.4 (2C), 142.6, 138.9 (2C), 134.4 (4C), 130.9, 129.4, 126.9, 126.5, 123.6 (2C), 121.9 (2C) ppm.

IR (neat)**:** ν = 3053, 3030, 1659, 1614, 1487, 1344, 1252, 982, 754, 692 cm^{-1}.

HRMS (EI): calculated for $C_{20}H_{16}N_2O^+ = [M^+]$: *m*/*z* = 300.1257, found: *m*/*z* =300.1268.

(*E*)- *N*, *N*-diphenyl-3-pyridin4-yl-acrylamide (343)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.20 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.00 equiv) in THF (10 ml). The mixture was stirred for 1 h and 4-pyridyl carboxaldehyde (502 mg, 4.70 mmol, 0.95 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **343** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 1.10 g (78%).

Mp: 144–145 °C

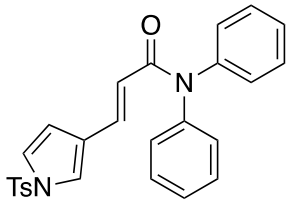
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 6.1 Hz, 2H), 7.69 (d, *J* = 15.5 Hz, 1H), 7.52–7.35 (m, 5H), 7.32–7.30 (m, 3H), 7.30–7.28 (m, 2H), 7.20 (d, *J* = 6.1 Hz, 2H), 6.65 (d, *J* = 15.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2, 150.5 (4C), 142.4 (2C), 142.3, 139.6 (2C), 129.3 (2C), 126.5 (2C), 124.3 (2C), 121.8 (4C), ppm.

IR (neat)**:** ν = 3057, 1657, 1489, 1344, 1250, 991, 709 cm^{-1}.

HRMS (EI): calculated for $C_{20}H_{16}ON_2^+$ = [M^+]: *m*/*z* = 300.1257, found: *m*/*z* = 300.1234.

(*E*)-*N*, *N*-Diphenyl-3-[1-(Toluene-4-sulfonyl)-pyrrole-2-yl]prop-2-enamide (344)



To a stirred slurry of sodium hydride (79.5 mg, 3.46 mmol, 1.20 equiv) in THF (10 ml) at -20 °C under an argon atmosphere was added phosphonate **339** (1.00 g, 2.88 mmol, 1.00 equiv) and the solution stirred for 1 h. The solution was warmed to 0 °C and 1-(4-tolylsulfonyl)pyrrole-2-carboxaldehyde (683 mg, 2.74 mmol, 0.95 equiv) was added in THF (5 ml) and the solution warmed to ambient and stirred for 12 h. Ammonium chloride (10 ml, sat. aq.) was added and the mixture was extracted with DCM (3 x 20 ml) and washed with brine (20 ml). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystallisation from diethyl ether afforded **344** as a tan solid, which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Colourless solid

Yield: 620 mg (51%).

Mp: 184–185 °C.

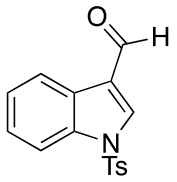
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 15.3 Hz, 1H), 7.77 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.43 (dd, *J* = 3.2, 1.6 Hz, 1H), 7.38–7.32 (m, 4H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.29–7.19 (m, 6H), 6.37–6.33 (m, 1H), 6.22–6.20 (m, 1H), 6.19 (d, *J* = 15.3 Hz, 1H), 2.41 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 145.3, 142.7 (2C), 135.7, 131.3, 130.2 (4C), 130.0, 129.2, 127.5, 127.3 (4C), 126.8, 125.2 (2C), 119.4 (2C), 114.9 (2C), 112.1, 21.7 ppm.

IR (neat)**:** ν = 3136, 3119, 2365, 1653, 1587, 1364, 1179, 671, 582 cm^{-1}.

HRMS (EI): calculated for $C_{26}H_{22}O_3N_2S^+$ = [M^+]: *m*/*z* = 442.1346, found: *m*/*z* = 442.1346.

1-Tosylindole-3-carboxaldehyde (345) [245]



To a solution of indole-3-carboxaldehyde (2.18 g, 15.0 mmol, 1.00 equiv) in DCM (30 ml) was added NEt_3 (4.20 ml, 30.0 mmol, 2.00 equiv) and the mixture cooled to 0 °C. Tosyl chloride (3.16 g, 16.6 mmol, 1.10 equiv) was added and the mixture stirred at ambient for 16 h. The solution was washed with HCl (10% aq 3 x 20 ml), followed by brine (50 ml) and dried over sodium sulfate. After filtration the solvent was removed under reduced pressure affording the titled compound.

Dark red solid

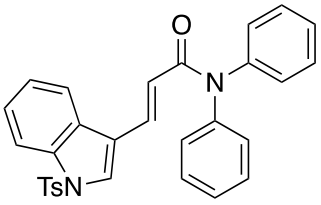
Yield 2.90 g (67%)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.11 (s, 1H), 8.28–8.25 (m, 2H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 2H), 7.45–7.36 (m, 2H), 7.33–7.28 (m, 2H), 2.39 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.4, 146.2, 136.3, 135.3, 134.4, 130.3 (2C), 127.3 (2C), 126.3, 126.3, 125.1, 122.6, 122.3, 113.3, 21.7 ppm.

IR (neat)**:** ν = 3132, 2849, 1663, 1368, 1161, 1126, 968, 758, 658 cm^{-1}.

(*E*)-*N*, *N*-Diphenyl-3-[1-(Toluene-4-sulfonyl)-indole-3-yl]prop-2-enamide (346)[245]



To a stirred slurry of sodium hydride (79.5 mg, 3.46 mmol, 1.20 equiv) in THF (10 ml) at -20 °C under an argon atmosphere was added phosphonate **339** (1.00 g, 2.88 mmol, 1.00 equiv) and the solution stirred for 1 h. The solution was warmed to 0 °C and 1-(4-tolylsulfonyl)indole-3-carboxaldehyde (818 mg, 2.74 mmol, 0.95 equiv) was added in THF (5 ml) and the solution warmed to ambient and stirred for 12 h. Ammonium chloride (10 ml, sat. aq.) was added and the mixture was extracted with DCM (3 x 20 ml) and washed with brine (20 ml). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystallisation from methanol afforded **346** as a tan solid, which was dried over molecular

sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Tan solid

Yield: 580 mg (43%).

Mp: 190–191 °C

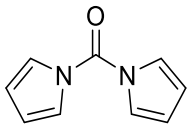
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 15.6 Hz, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.72 (s, 1H), 7.51–7.35 (m, 4H), 7.35–7.24 (m, 8H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 15.6 Hz, 1H), 2.33 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 145.4, 142.8 (2C), 135.6, 134.8, 133.5 (2C), 130.0 (4C), 129.3, 128.3, 127.9, 126.9 (4C), 125.3 (2C), 123.9 (2C), 120.3 (2C), 120.2 (2C), 118.9, 113.8, 21.6 ppm.

IR (neat)**:** ν = 3138, 3061, 2359, 1661, 1359, 1173, 1130, 980, 681 cm^{-1}.

HRMS (EI): calculated for $C_{30}H_{24}O_3N_2{}^{32}S^+$ = [M^+]: *m*/*z* = 492.1502, found: *m*/*z* = 492.1505.

Carbonyl dipyrrole (<u>347</u>)[246]



To a solution of pyrrole (4.40 ml, 64.4 mmol, 3.00 equiv) was added 1, 1' carbonyldiimidazole (3.47 g, 21.4 mmol, 1.00 equiv) and the suspension heated to 130 °C and stirred under nitrogen for 90 minutes before cooling. The black solution was dried *in vacuo* to a black tar. The residue was dissolved in EtOAc (50 ml), activated carbon (1 spatula) added and the mixture heated to reflux for 5 minutes before filtering through celite and washed with EtOAc (3 x 100 ml). The filtrate was washed with HCL (2 x 50 ml, 1 M) and brine (50 ml). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*.

Tan solid.

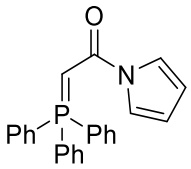
Yield: 1.98 g (56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 2.4 Hz, 4H), 6.39 (t, *J* = 2.4 Hz, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 148.0, 122.0 (4C), 113.3 (4C) ppm.

HRMS (EI): calculated for $C_9H_8ON_2^+$ = [M^+]: *m*/*z* = 160.0631, found: *m*/*z* = 160.0632.

1-(1H-Pyrrol-1-yl)-2-triphenylphosphoranylidene)ethanone (<u>348</u>)[247]



To a solution of methyltriphenylphosphonium bromide (12.9 g, 36.0 mmol, 3.00 equiv) in THF (36 ml) at 0 °C was added ^{n}BuLi (22.5 ml, 36.0 mmol, 3.00 equiv, 1.6 M) and the mixture stirred for 1 h. After cooling to -78 °C carbonyldipyrrole (1.92 g, 12.0 mmol, 1.00 equiv) in THF (18 ml) was added and the solution warmed to ambient over 15 h. Water (50 ml) was added and the mixture extracted with a mix of ethyl acetate/DCM (5:1) (3 x 100 ml) and the combined organic fractions dried over magnesium sulfate and the solvent removed.

Colourless solid

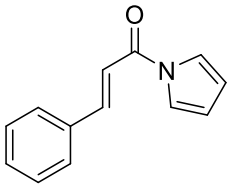
Yield: 1.40 g (56%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.78–7.67 (m, 6H), 7.64–7.57 (m, 3H), 7.55–7.47 (m, 6H), 7.38 (t, *J* = 2.3 Hz, 2H), 6.21 (t, *J* = 2.3 Hz, 2H), 3.75 (d, *J* = 19.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6 (d, *J* = 10.0 Hz), 133.2 (d, *J* = 10.5 Hz, 6C), 132.2 (3C), 131.9 (2C), 128.9 (d, *J* = 12.4 Hz, 6C) 126.75 (d, *J* = 92.3 Hz), 118.6 (2C), 109.5 (3C) ppm.

^{31}P NMR (202 MHz, $CDCl_3$): δ = 18.5 ppm

***N*-pyrrolecinnamide (<u>349</u>)[248]**



To a stirred solution of pyrrolylmethylenetriphenylphosphorane (1.39 g, 6.50 mmol, 1.30 equiv) in toluene (15 ml) at ambient temperature under an argon atmosphere was added benzaldehyde (508 ml, 5.00 mmol, 1.00 equiv) and the mixture heated to reflux and stirred for 48 h. To the solution was added water (20 ml) and the organic layer separated and washed with brine (10 ml). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystalisation from methanol yielded a colourless solid which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 780 mg (61%).

Mp: 110–110.5 °C

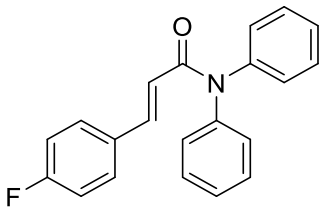
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 15.5 Hz, 1H), 7.69–7.63 (m, 2H), 7.50 (t, *J* = 2.4 Hz, 2H), 7.48–7.47 (m, 3H), 7.18 (d, *J* = 15.5 Hz, 1H), 6.39 (d, *J* = 2.7 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.0, 147.6 (2C), 134.3, 131.0, 129.1 (2C), 128.5 (2C), 119.3, 115.8, 113.4 (2C) ppm.

IR (neat)**:** ν = 3142, 1688, 1622, 1346, 1125, 738 cm^{-1}.

HRMS (EI): calculated for $C_{13}H_{11}ON^+$ = [M^+]: *m*/*z* = 197.0835, found: *m*/*z* = 197.0839.

4-Fluorocinnamic acid-*N*, *N*-diphenylamide (<u>350</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.20 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.05 equiv) in THF (10 ml). The mixture was stirred for 1 h and 4-fluorobenzaldehyde (596 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **350** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 1.05 g (70%).

Mp: 180–181 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 15.5 Hz, 1H), 7.49–7.35 (m, 4H), 7.35–7.30 (m, 3H) 7.30–7.21 (m, 5H), 6.99 (t, *J* = 8.6 Hz, 2H), 6.39 (d, *J* = 15.5 Hz, 1H) ppm.

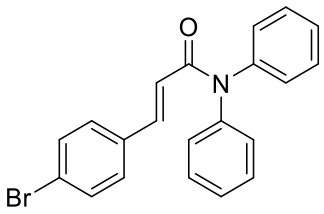
^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.0, 164.6, 162.6 (d, *J* = 250.5 Hz), 142.8 (2C), 141.4 (2C), 131.4 (d, *J* = 3.5 Hz), 129.8 (2C), 129.7 (2C), 129.3 (2C), 126.9, 119.5 (d, *J* = 2.0 Hz, 2C), 115.9 (2C), 115.8 (2C) ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -110.50 ppm.

IR (neat)**:** ν = 3067, 1661, 1487, 1354, 829, 696 cm^{-1}.

HRMS (EI): calculated for $C_{21}H_{16}ONF^+$ = [M^+]: *m*/*z* = 317.1210, found: *m*/*z* = 317.1219.

4-Bromocinnamic acid-*N*, *N*-diphenylamide (<u>351</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.28 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.06 equiv) in THF (10 ml). The mixture was stirred for 1 h and 4-chlorobenzaldehyde (675 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **351** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 1.22 g (67%).

Mp: 174–175 °C

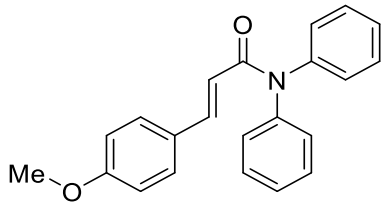
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 15.5 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.41– 7.34 (m, 4H), 7.33–7.24 (m, 6H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.46 (d, *J* = 15.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 142.7, 141.2 (2C), 134.0 (2C), 132.0 (4C), 129.4 (4C), 127.0, 123.9 (2C), 120.5 (2C) ppm.

IR (neat)**:** ν = 3707, 2967, 1659, 1487, 1346, 1007, 704 cm^{-1}.

HRMS (EI): calculated for $C_{21}H_{16}ON^{79}Br^{+}$ = [M^{+}]: *m*/*z* = 377.0410, found: *m*/*z* = 377.0411.

4-Methoxycinnamic acid-*N*, *N*-diphenylamide (<u>352</u>)[239]



To a stirred solution of 4-methoxycinnamic acid (3.56 g, 20.0 mmol, 1.00 equiv) in DCM (20 ml) at ambient temperature under an argon atmosphere was added thionyl chloride (4.80 g, 40.0 mmol, 2.00 equiv) and the mixture stirred for 3 h at reflux. The solvent and excess thionyl chloride were removed in vacuo and the solid redissolved in DCM (20 ml). To the solution was added diphenylamine (3.38 g, 20.0 mmol, 1.00

equiv) and the mixture stirred for 15 h. The solvent was removed in vacuo and the solid recrystalised from ethanol to afford a pale yellow solid which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid dried in high vacuum before use in catalysis.

Pale yellow solid

Yield: 1.8 g (55%).

Mp: 132–133 °C (Lit.: 94–96 °C).

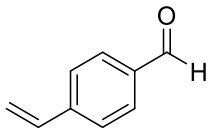
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 15.5 Hz, 1H), 7.44–7.33 (m, 4H), 7.32–7.20 (m, 8H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.35 (d, *J* = 15.5 Hz, 1H), 3.79 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 161.0, 143.0 (2C), 142.3 (2C), 129.6 (4C), 129.2, 127.9 (2C), 127.6, 126.7, 117.4 (2C), 114.2 (4C), 55.3 ppm.

IR (neat)**:** ν = 3009, 2381, 1653, 1593, 1489, 1240, 1153, 992, 755 cm^{-1}.

HRMS (EI): calculated for $C_{22}H_{19}O_2N^+ = [M^+]$: *m*/*z* = 329.1410, found: *m*/*z* = 329.1400.

4-Formylstyrene (353)[249]



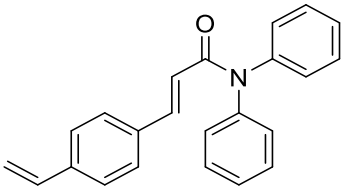
4-Bromostyrene (3.00 g, 16.2 mmol, 1.00 equiv) was dissolved in THF (60 ml) and cooled to -78 °C. ^{n}BuLi (7.2 ml, 18.0 mmol, 1.13 equiv, 1.6 M) was added dropwise and the reaction stirred for 2 h at -78 °C before DMF (1.40 ml, 18.0 mmol, 1.13 equiv) was added and the reaction stirred for a further 14 h. Ethyl acetate (25 ml) and ammonium chloride (25 ml, sat. aq.) was added and the organic layer separated. The mixture was extracted with ethyl acetate (2 x 25 ml) and the combined organic extracts dried over magnesium sulfate and the solvent removed *in vacuo* which was used without further purification.

Pale yellow liquid.

Yield: 2.00 g (93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.01 (s, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 6.79 (dd, *J* = 17.6, 10.9 Hz, 1H), 5.93 (d, *J* = 17.6 Hz, 1H), 5.46 (d, *J* = 10.9 Hz, 1H) ppm.

4-Vinylcinnamic acid-*N*, *N*-diphenylamide (<u>354</u>)



To a stirred slurry of sodium hydride (227 mg, 9.48 mmol, 1.20 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (2.70 g, 7.90 mmol, 1.05 equiv) in THF (10 ml). The mixture was stirred for 1 h and 4-vinylbenzaldehyde (1.00 g, 7.57 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **354** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 450 mg (18%).

Mp: 143–144 °C

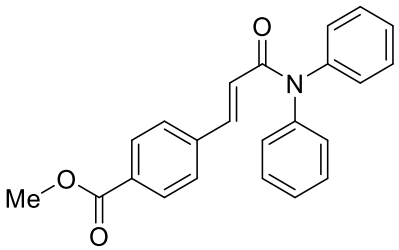
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 15.5 Hz, 1H), 7.41–7.36 (m, 4H), 7.36–7.28 (m, 5H), 7.29–7.25 (m, 5H), 6.68 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.47 (d, *J* = 15.5 Hz, 1H), 5.76 (dd, *J* = 17.6, 0.8 Hz, 1H), 5.28 (dd, *J* = 17.6, 0.8 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 142.8 (2C), 142.1 (2C), 139.0, 136.2 (2C), 134.6, 129.3, 128.2 (4C), 127.1, 126.6 (4C), 119.6 (2C), 114.9 (2C) ppm.

IR (neat)**:** ν = 3096, 1663, 1491, 1261, 766, 697 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{19}ON^{+}$ = [M^{+}]: *m*/*z* = 325.1461, found: *m*/*z* = 325.1469.

4-Methoxybenzocinnamic acid-*N*, *N*-diphenylamide (<u>355</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.20 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.00 equiv) in THF (10 ml). The mixture was stirred for 1 h and methyl 4-formylbenzoate (788 mg, 4.70 mmol, 0.95 equiv) in THF (10

ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **355** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 1.38 g (82%).

Mp: 174–175 °C

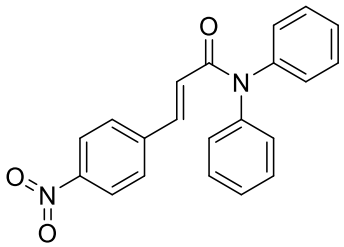
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 6.1 Hz, 2H), 7.69 (d, *J* = 15.5 Hz, 1H), 7.52–7.35 (m, 5H), 7.32–7.30 (m, 3H), 7.30–7.28 (m, 2H), 7.20 (d, *J* = 6.1 Hz, 2H), 6.65 (d, *J* = 15.5 Hz, 1H) 4.15 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 165.7, 142.6, 141.2 (2C), 139.4 (2C), 130.9 (2C), 130.0 (4C), 129.4 (2C), 127.8 (4C), 126.7, 122.2 (2C), 52.2 ppm.

IR (neat)**:** ν = 3024, 1707, 1653, 1362, 1279, 1016, 698 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{19}O_3N^+ = [M^+]$: *m*/*z* = 357.1359, found: *m*/*z* = 357.1355.

4-Nitrocinnamic acid-*N*, *N*-diphenylamide (<u>356</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.20 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.00 equiv) in THF (10 ml). The mixture was stirred for 1 h and 4-nitrobenzaldehyde (717 mg, 4.70 mmol, 0.95 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **356** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 980 g (61%).

Mp: 166–168 °C

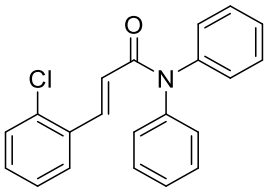
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 15.6 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.45–7.35 (m, 5H), 7.34–7.27 (m, 5H), 6.59 (d, *J* = 15.6 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.2, 148.1, 142.4, 141.3 (2C), 139.7 (2C), 129.5 (2C), 128.5 (4C), 126.7, 124.1 (4C), 124.0 (4C) ppm.

IR (neat)**:** ν = 3105, 1661, 1518, 1345, 960, 698 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{19}O_3N^+$ = [M^+]: *m*/*z* = 344.1155, found: *m*/*z* = 344.1153.

2-Chlorocinnamic acid-*N*, *N*-diphenylamide (<u>357</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.20 equiv) in THF (20 ml) at 0 ° was added phosphonate **339** (1.74 g, 5.00 mmol, 1.05 equiv) in THF (10 ml). The mixture was stirred for 1 h and 2-chlorobenzaldehyde (675 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **357** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 540 mg (35%).

Mp: 161–162 °C

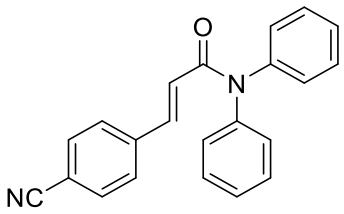
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 15.5 Hz, 1H), 7.47–7.33 (m, 5H), 7.33–7.26 (m, 7H) 7.22 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 6.48 (d, *J* = 15.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 142.7, 138.6 (2C), 134.9, 133.5, 130.4 (4C), 130.1 (2C), 129.3, 127.8 (4C), 126.8 (2C), 122.6 (2C) ppm.

IR (neat)**:** ν = 3055, 2361, 1655, 1487, 1352, 1273, 982, 762, 691 cm^{-1}.

HRMS (EI): calculated for $C_{21}H_{16}ON^{35}Cl^+$ = [M^+]: *m*/*z* = 333.0915, found: *m*/*z* = 333.0914.

4-Cyanocinnamic acid-*N*, *N*-diphenylamide (<u>358</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.20 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.05 equiv) in THF (10 ml). The mixture was stirred for 1 h and 4-cyanobenzaldehyde (629 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **358** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 1.10 g (67%).

Mp: 184–185 °C

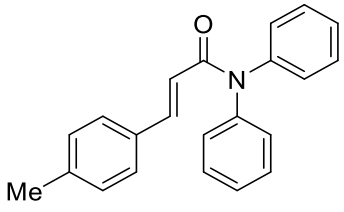
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 15.6 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.43–7.36 (m, 6H), 7.32–7.22 (m, 6H), 6.55 (d, *J* = 15.6 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.3, 142.5 (2C), 140.2 (2C), 139.4 (2C), 132.5 (4C), 129.4, 128.3 (4C), 126.6, 123.3 (2C), 118.5, 112.8 (2C) ppm.

IR (neat)**:** ν = 3067, 2226, 1657, 1489, 1348, 1250, 698 cm^{-1}.

HRMS (EI): calculated for $C_{22}H_{16}ON_2^+$ = [M^+]: *m*/*z* = 350.1414, found: *m*/*z* = 350.1416.

4-Methylcinnamic acid-*N*, *N*-diphenylamide (<u>359</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.28 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.06 equiv) in THF (10 ml). The mixture was stirred for 1 h and 4-methylbenzaldehyde (577 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and

DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **359** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 1.15 g (77%).

Mp: 165–165.5 °C

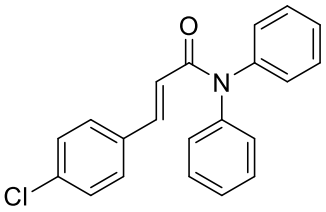
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 15.5 Hz, 1H), 7.44–7.33 (m, 4H), 7.30– 7.21 (m, 8H), 7.12–7.10 (d, *J* = 8.0 Hz, 2H), 6.44 (d, *J* = 15.5 Hz, 1H), 2.33 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4, 142.9, 142.6 (2C), 140.0 (2C), 132.4 (2C), 129.5 (4C), 129.2, 128.0 (4C), 127.7, 126.8, 118.8 (2C), 21.4 ppm.

IR (neat)**:** ν = 3049, 1657, 1487, 1356, 1254, 984, 812, 693 cm^{-1}.

HRMS (EI): calculated for $C_{22}H_{19}ON^+$ = [M^+]: *m*/*z* = 313.1461, found: *m*/*z* = 313.1466.

4-Chlorocinnamic acid-*N*, *N*-diphenylamide (<u>360</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.28 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.06 equiv) in THF (10 ml). The mixture was stirred for 1 h and 4-chlorobenzaldehyde (675 mg, 4.7 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **360** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 850 mg (53%).

Mp: 158–159 °C

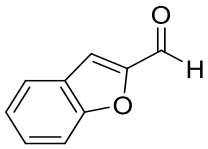
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 15.5 Hz, 1H), 7.50–7.37 (m, 4H), 7.36–7.21 (m, 10H), 6.47 (d, *J* = 15.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 142.7, 141.2 (2C), 135.6, 133.6 (2C), 129.3, 129.1 (4C), 129.0 (4C), 127.0 (2C), 120.4 (2C) ppm.

IR (neat)**:** ν = 3063, 1661, 1487, 1346, 976, 756, 700 cm^{-1}.

HRMS (EI): calculated for $C_{21}H_{16}ON^{35}Cl^+$ = [M^+]: *m*/*z* = 333.0915, found: *m*/*z* = 333.0914.

2-Formylbenzofuran (<u>361</u>)[250]



Benzofuran (2.50 g, 21.2 mmol, 1.00 equiv) was dissolved in THF (60 ml) and cooled to -78 °C. ^{n}BuLi (10.1 ml, 25.4 mmol, 1.13 equiv, 2.5 M) was added dropwise and the reaction stirred for 2 h at -78 °C before DMF (3.26 ml, 42.2 mmol, 2.00 equiv) was added and the reaction stirred for a further 14 h. Ethyl acetate (25 ml) and ammonium chloride (25 ml, sat. aq.) was added and the organic layer separated. The mixture was extracted with ethyl acetate (2 x 25 ml) and the combined organic extracts dried over magnesium sulfate and the solvent removed *in vacuo*.

Pale yellow liquid.

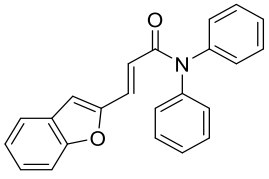
Yield: 1.92 g (62%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.90 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 1.0 Hz, 1H), 7.55 (t, *J* = 8.4 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.8, 156.3, 152.7, 129.2, 126.7, 124.2, 123.7, 117.8, 112.7 ppm.

IR (neat)**:** ν = 2936, 1678, 1557, 1288, 1119, 947, 831, 733 cm^{-1}.

4-(2-Benzofuryl)cinnamic acid-*N*, *N*-diphenylamide (<u>362</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.28 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.06 equiv) in THF (10 ml). The mixture was stirred for 1 h and 2-formylbenzofuran (700 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and

DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **362** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 740 mg (46%).

Mp: 192–194 °C

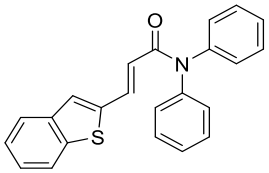
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 15.2 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.47–7.34 (m, 5H), 7.33–7.26 (m, 7H), 7.20 (t, *J* = 7.7 Hz, 1H), 6.87 (s, 1H), 6.63 (d, *J* = 15.2 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 155.4, 153.1 (2C), 142.7, 129.7 (2C), 129.3, 128.5 (2C), 127.0, 126.1 (2C), 123.2 (2C), 121.6 (2C), 120.3 (2C), 111.3 (2C), 110.6 (2C) ppm.

IR (neat)**:** ν = 3051, 2357, 1665, 1620, 1489, 1271, 827, 731 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{17}O_2N^+$ = [M^+]: *m*/*z* = 339.1254, found: *m*/*z* = 339.1257.

4-(2-Benzothiophenyl)cinnamic acid-*N*, *N*-diphenylamide (363)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.28 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.06 equiv) in THF (10 ml). The mixture was stirred for 1 h and 2-formylbenzothiophene (761 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **363** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 820 mg (49%).

Mp: 180–181 °C

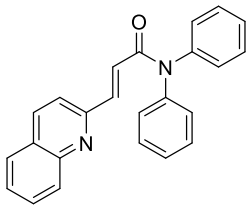
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 15.1 Hz, 1H), 7.78–7.69 (m, 2H), 7.49–7.38 (m, 5H), 7.38–7.29 (m, 8H), 7.37 (d, *J* = 15.1 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.7, 142.6 (2C), 140.3, 140.0, 139.7, 135.7 (2C), 129.3 (2C), 127.9 (2C), 126.9, 125.9 (2C), 124.8 (2C), 124.3 (2C), 122.3 (2C), 121.3 (2C) ppm.

IR (neat)**:** ν = 3688, 2970, 1655, 1356, 1152, 1037, 988, 766 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{17}ONS^+$ = [M^+]: *m*/*z* = 355.1025, found: *m*/*z* = 355.1015.

4-(2-Quinoline)cinnamic acid-*N*, *N*-diphenylamide (<u>364</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.28 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.06 equiv) in THF (10 ml). The mixture was stirred for 1 h and 2-quinolinecarboxaldehyde (754 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **364** as pale purple needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Pale purple solid

Yield: 580 mg (41%).

Mp: 195–196 °C

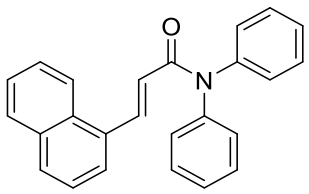
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 15.4 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.68 (t, *J* = 6.9 Hz, 1H), 7.51 (d, *J* = 6.9 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.41–7.36 (m, 2H), 7.35–7.26 (m, 6H), 7.09 (d, *J* = 15.4 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.8, 153.9, 148.3, 142.7, 142.2 (2C), 136.5 (2C), 129.9 (4C), 129.3, 127.9 (2C), 127.4, 127.0 (4C), 125.3 (2C), 120.7 (2C) ppm.

IR (neat)**:** ν = 3204, 1641, 1576, 1356, 1132, 823, 734, 691 cm^{-1}.

HRMS (EI): calculated for $C_{24}H_{18}ON_2^+$ = [M^+]: *m*/*z* = 350.1414, found: *m*/*z* = 350.1416.

4-(1-Napthyl)cinnamic acid-*N*, *N*-diphenylamide (<u>365</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.28 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.06 equiv) in THF (10 ml). The mixture was stirred for 1 h and 1-napthaldehyde (750 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **365** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 620 mg (38%).

Mp: 194–195 °C

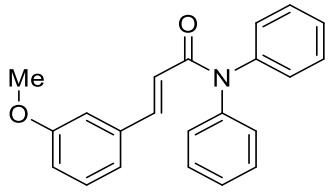
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, *J* = 15.3 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 7.83 (t, *J* = 8.3 Hz, 2H), 7.53 (d, *J* = 20.9, 7.8 Hz, 2H), 7.47–7.35 (m, 7H), 7.34–7.24 (m, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 142.8 (2C), 139.7 (2C), 133.6, 132.7, 131.5, 129.9 (2C), 129.3, 128.6 (2C), 126.7 (2C), 126.2 (2C), 125.3 (2C), 124.8 (2C), 123.7 (2C), 122.7 (2C) ppm.

IR (neat)**:** ν = 3059, 2381, 1681, 1489, 1331, 976, 772, 693 cm^{-1}.

HRMS (EI): calculated for $C_{25}H_{19}ON^{+}$ = [M^{+}]: *m*/*z* = 349.1461, found: *m*/*z* = 349.1472.

3-Methoxycinnamic acid-*N*, *N*-diphenylamide (<u>366</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.28 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.06 equiv) in THF (10 ml). The mixture was stirred for 1 h and 3-anisaldehyde (585 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was

added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **366** as colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 1.25 g (81%).

Mp: 163–164 °C

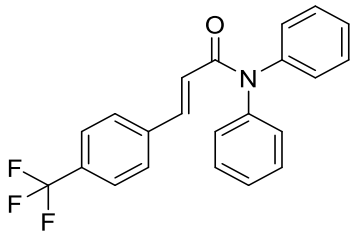
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 15.5 Hz, 1H), 7.46–7.33 (m, 4H), 7.31–7.25 (m, 5H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.89–6.84 (m, 2H), 6.46 (d, *J* = 15.5 Hz, 1H), 3.77 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 159.8, 142.8 (2C), 142.5, 136.6, 129.7 (2C), 129.3, 126.9, 120.5 (4C), 120.2, 115.1 (2C), 113.5 (4C), 55.3 ppm.

IR (neat)**:** ν = 3059, 2835, 1657, 1489, 1350, 1267, 985, 777, 694 cm^{-1}.

HRMS (EI): calculated for $C_{22}H_{19}O_2N^+$ = [M^+]: *m*/*z* = 329.1410, found: *m*/*z* = 329.1416.

4-Trifluoromethylcinnamic acid-*N*, *N*-diphenylamide (<u>367</u>)



To a stirred slurry of sodium hydride (144 mg, 6.00 mmol, 1.28 equiv) in THF (20 ml) at 0 °C was added phosphonate **339** (1.74 g, 5.00 mmol, 1.06 equiv) in THF (10 ml). The mixture was stirred for 1 h and 4-trifluoromethylbenzaldehyde (817 mg, 4.70 mmol, 1.00 equiv) in THF (10 ml) was added. The mixture was stirred for 15 h then ammonium chloride (10 ml, sat. aq.) and DCM (10 ml) was added and the organic layer separated, washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **367** as pale colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 515 mg (30%).

Mp: 143–144 °C

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 15.5 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.35–7.29 (m, 4H), 7.24–7.19 (m, 6H), 6.48 (d, *J* = 15.5 Hz, 1H) ppm.

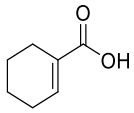
^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.6, 142.6, 140.7 (4C), 138.5, 131.2 (q, *J* = 32.9 Hz), 129.4 (2C), 128.1 (4C), 127.1, 125.7 (q, *J* = 4.0 Hz, 2C), 125.0, 124.0 (q, *J* = 272.6 Hz), 122.8, 122.3, 120.6 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -62.8 ppm

IR (neat)**:** ν = 3065, 2361, 2160, 1661, 1491, 1310, 1123, 833, 698 cm^{-1}.

HRMS (EI): calculated for $C_{22}H_{16}ONF_3^+$ = [M^+]: *m*/*z* = 367.1179, found: *m*/*z* = 367.1186.

Cyclohexene-1-carboxylic acid (368)[251]



To a solution of cyclohexanone (5.00 g, 50.0 mmol, 1.00 equiv) in *tert*-butanol (200 ml) was added LiOH (43.2 g, 1.02 mol, 2.00 equiv in 40 ml H_2O) and benzyltriethylammonium bromide (1.14 g, 5.00 mmol, 0.10 equiv). The mixture was stirred for 5 minutes after which bromoform (51.5 g, 200 mmol, 4.00 equiv) was added using a pressure equalising dropping funnel. The reaction temperature was maintained below 50 °C and stirred for 24 h. Water (200 ml) was added, shaken vigerously and separated. The aqueous layer was further washed with toluene (2 x 100 ml) before acidification to pH 1 using HCl (20 %). The oil that separated was dissolved in toluene and the aqueous extracted with toluene (2 x 50 ml). The combined organic layers were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to afford a pale brown oil of sufficient purity.

Colourless solid

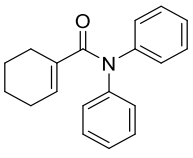
Yield: 6.15 g (97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.80 (br s, 1H), 7.16 (tt, *J* = 3.8, 1.7 Hz, 1H), 2.33–2.21 (m, 4H), 1.75–1.61 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.0, 142.6, 129.7, 26.0, 23.7, 22.0, 21.3 ppm.

IR (neat)**:** ν = 2934, 1682, 1278, 922 cm^{-1}.

Cyclohexene-1-diphenylamide (369)



To a solution of cyclohexene-1-carboxylic acid (2.00 g, 15.9 mmol, 1.00 equiv) in DCM (15 ml) was added oxalyl chloride (2.02 g, 15.9 mmol, 1.00 equiv) and the mixture stirred at ambient

temperature overnight. Diphenylamine (2.42 g, 14.3 mmol, 0.90 equiv) was added followed by triethylamine (1.91 g, 15.9 mmol, 1.00 equiv). The mixture was stirred at ambient overnight before water (20 ml) was added. The reacton mixture was separated and washed with brine (25 ml) dried over magnesium sulfate and the solvent removed *in vacuo*. Recrystalisation from ethanol afforded **1a** as pale colourless needle crystals, which were dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the liquid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 320 mg (8%).

Mp: 161.1–161.8 °C

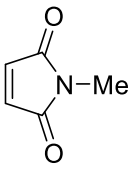
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.31 (m, 4H), 7.31–7.08 (m, 6H), 4.24–4.11 (m, 1H), 3.12 (dt, *J* = 8.5, 4.1 Hz, 1H), 2.27–2.13 (m, 1H), 2.13–2.00 (m, 1H), 1.91–1.80 (m, 1H), 1.80–1.68 (m, 1H), 1.64–1.57 (m, 1H), 1.57–1.50 (m, 1H), 1.44–1.31 (m, 1H), 1.31–1.16 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 143.1 (2C), 129.2 (br 4C), 128.9 (br 4C), 127.1, 126.1, 59.4, 44.7, 33.5, 24.5, 22.9, 21.9 ppm.

IR (neat)**:** ν = 3056, 2938, 1655, 1489, 1275, 758, 694 cm^{-1}.

3.3.4 Other Michael Amides

_N_-Methylmaleimide (300)[252]



To a solution of *N*-Methylmaleamic acid (8.00 g, 62.0 mmol, 1.00 equiv) in acetic anhydride (150 ml) was added sodium acetate (9.80 g, 119.4 mmol, 1.90 equiv) and the mixture refluxed for 20 h. After cooling the mixture was quenched with saturated sodium bicarbonate, extracted with chloroform (3 x 150 ml) and the solvent removed *in vacuo*. The solid was recrystalised from ethyl acetate yielding colourless crsytasls which were was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid dried in high vacuum before use in catalysis.

Colourless solid

Yield: 900 mg (55%).

Mp: 91–92 °C (Lit.: 92.1–93.1 °C).

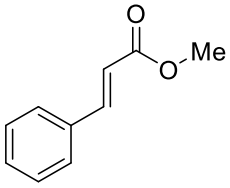
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.71 (s, 2H), 3.02 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.8 (2C), 134.2 (2C), 23.7 ppm.

IR (neat)**:** ν = 3094, 2361, 1692, 1437, 937, 692 cm^{-1}.

HRMS (EI): calculated for $C_5H_5O_2N^+ = [M^+]$: *m*/*z* = 111.0315, found: *m*/*z* = 111.0319.

***(E)-Methylcinnamate* (370)[253]**



To a stirred solution of *trans*-cinnamic acid (1.48 g, 10.0 mmol, 1.00 equiv) in DCM (25 ml) at ambient temperature under an argon atmosphere was added thionyl chloride (2.38 g, 20.0 mmol, 2.00 equiv) and the solution stirred for 4 h. The solvent and excess thionyl chloride was removed *in vacuo* affording a colourless solid which was dissolved in toluene (20 ml). Methanol (1 ml, 40 mmol, 4 equiv) was added followed by triethylamine (1.01 g, 10.0 mmol, 1.00 equiv) and the reaction stirred for 15 h. Water (20 ml) was added and the mixture was extracted with DCM (3 x 20 ml). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystallisation from methanol afforded **370** as a colourless solid, which was dried over molecular sieves (4 Å) in THF at room

temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Colourless solid

Yield: 1.46 g (90%).

Mp: 33–34 °C (Lit.: 33–34 °C).[246]

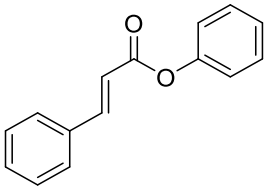
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 16.1 Hz, 1H), 7.59–7.52 (m, 2H), 7.45–7.36 (m, 3H), 6.47 (d, *J* = 16.1 Hz, 1H), 3.83 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.4, 144.9, 134.4, 130.3, 128.9 (2C), 128.1 (2C), 117.8, 51.7 ppm.

IR (neat)**:** ν = 3034, 1724, 1636, 1306, 1144, 970, 762, 679 cm^{-1}.

HRMS (EI): calculated for $C_{10}H_{10}O_2^+$ = [M^+]: *m*/*z* = 162.0675, found: *m*/*z* = 162.0676.

***(E)-Phenylcinnamate* (371)[255]**



To a stirred solution of *trans*-cinnamic acid (1.48 g, 10.0 mmol, 1.00 equiv) in DCM (25 ml) at ambient temperature under an argon atmosphere was added thionyl chloride (2.38 g, 20.0 mmol, 2.00 equiv) and the solution stirred for 4 h. The solvent and excess thionyl chloride was removed *in vacuo* affording a colourless solid which was dissolved in toluene (20 ml). Phenol (1.88 g, 20.0 mmol, 2.00 equiv) was added followed by triethylamine (1.01 g, 10.0 mmol, 1.00 equiv) and the reaction stirred for 15 h. Water (20 ml) was added and the mixture was extracted with DCM (3 x 20 ml). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystallisation from methanol afforded **371** as a colourless solid, which was dried over molecular sieves (4 Å) in THF at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Colourless solid

Yield: 1.85 g (82%).

Mp: 74–75 °C (Lit.: 74–75 °C).[248]

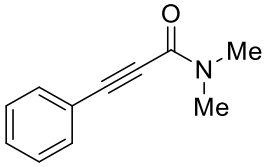
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 16.0 Hz, 1H), 7.70–7.51 (m, 2H), 7.52–7.31 (m, 5H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 6.64 (d, *J* = 16.0 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4, 150.8, 146.6, 134.2, 130.7, 129.4 (2C), 129.0 (2C), 128.3 (2C), 125.8, 121.6 (2C), 117.4 ppm.

IR (neat)**:** ν = 3067, 2943, 1711, 1636, 1437, 1314, 1165, 982, 772, 689 cm^{-1}.

HRMS (EI): calculated for $C_{15}H_{12}O_2^+$ = [M^+]: *m*/*z* = 224.0832, found: *m*/*z* = 224.0831.

***N*,*N*-Dimethyl-3-phenylpropiolamide (<u>314</u>)[257]**



To a stirred solution of phenyl acetylene (2.24 g, 22.0 mmol, 1.05 equiv) in THF (15 mL) at –78 °C under an argon atmosphere was added ^{n}BuLi (1.6 M in hexane; 15.6 mL, 25.0 mmol, 1.20 equiv) dropwise. The reaction was stirred at ambient for 30 min before being cooled –78 °C. Dimethylcarbamoyl chloride (1.93 mL, 21.0 mmol, 1.00 equiv) was added dropwise and the mixture stirred for 1 h. Ammonium chloride (sat aq.; 10 mL) was added, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystallisation from methanol afforded **315** as a tan solid, which was dried over molecular sieves (4 Å) in diethyl ether at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Tan solid.

Yield: 2.21 g (65%).

Mp: 94–96 °C (Lit.: 97–99 °C).[258]

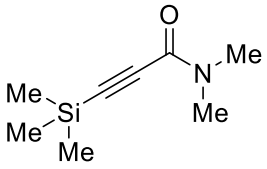
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60–7.48 (m, 2H), 7.46–7.29 (m, 3H), 3.28 (s, 3H), 3.02 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.6, 132.3, 130.0 (2C), 128.5 (2C), 120.6, 90.1, 81.6, 38.4, 34.2 ppm.

IR (neat)**:** ν = 2928, 2208, 1620, 1491, 1395, 1253, 1136, 783, 729, 692 cm^{-1}.

HRMS (EI): calculated for $C_{11}H_{11}NO^+$ = [M^+]: *m*/*z* = 173.0835, found: *m*/*z* =173.0829.

***N*, *N*-Dimethyl-3-trimethylsilylpropiolamide (315)[259]**



To a stirred solution of trimethylsilyl acetylene (2.16 g, 22.0 mmol, 1.05 equiv) in THF (15 mL) at –78 °C under an argon atmosphere was added ^{n}BuLi (1.6 M in hexane; 15.6 mL, 25.0 mmol, 1.20 equiv) dropwise. The reaction was stirred at ambient for 30 min before being cooled –78 °C. Dimethylcarbamoyl chloride (1.93 mL, 21.0 mmol, 1.00 equiv) was added dropwise and the mixture stirred for 1 h. Ammonium chloride (sat aq.; 10 mL) was added, and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystallisation from methanol afforded **315** as a tan solid, which was dried over molecular sieves (4 Å) in diethyl ether at room temperature for 18 h in a glovebox. After filtration, the solvent was removed *in vacuo*, and the solid ground and dried in high vacuum before use in catalysis.

Tan solid.

Yield: 1.00 g (28%).

Mp: 43–44 °C (Lit.: 42–43 °C).

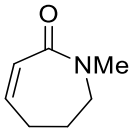
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.21 (s, 3H), 2.97 (s, 3H), 0.24 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.0, 97.1, 96.1, 38.3, 34.0, –0.7 ppm (3C).

IR (neat)**:** ν = 2961, 2932, 1618, 1499, 1393, 1251, 1153, 764, 860 cm^{-1}.

HRMS (EI): calculated for $C_8H_{15}NOSi^+$ = [M^+]: *m*/*z* = 169.0917, found: *m*/*z* = 169.0926.

1-Methyl-1,5,6,7-tetrahydro-2H-azepin-2-one (302)[260]



To a solution of diphenyldiselenide (1.56 g, 4.50 mmol, 1.10 equiv) in THF (20 ml) under argon was added bromine (791 mg, 4.50 mmol, 1.10 equiv) and the mixture stirred for 1 h. In a separate flask $HN^{i}Pr_2$ (1.09 g, 10.8 mmol, 1.20 equiv) in THF (30 ml) was cooled to 0 °C and ^{n}BuLi (6.65 ml, 1.6 M, 9.00 mmol, 1.10 equiv) added dropwise and the mixture stirred for 1 h. The solution was cooled to -78 °C and *N*-methylcaprolactame (1.14 g, 9.00 mmol, 1.00 equiv) was added and the reaction slowly warmed to ambient temperature and stirred for 1 h. The mixture was recooled to -78 °C and the phenyl selenylbromide solution added dropwise. The reaction was allowed to warm to ambient and stirred for 16 h. The mixture was poured onto ice water (50 ml) and extracted with diethylether (3 x 50 ml). The combined organics were

dried over magnesium sulfate and the solvent removed in vacuo affording a brown solid. The solid was dissolved in DCM (50 ml) and mCPBA (2.33 g, 13.5 mmol, 1.50 equiv) was added cautiously. The reaction was stirred at ambient for 24 h and the solvent removed in vacuo affording the crude product which was purified using flash column chromatography eluting EtOAc:hexane (50:1).

Pale yellow liquid

Yield 150 mg (13%)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.09 (dt, *J* = 12.1, 5.1 Hz, 1H), 5.86 (dt, *J* = 12.1, 1.7 Hz, 1H), 3.30–3.24 (m, 2H), 2.95 (s, 3H), 2.23 (tdd, *J* = 5.2, 1.7 Hz, 2H), 1.90–1.85 (m, 2H), 1.65–1.59 (m, 1H), 1.55 (td, *J* = 10.2, 5.5 Hz, 1H) ppm.

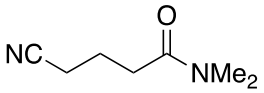
^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 138.0, 126.5, 49.1, 35.7, 28.1, 27.6 ppm.

IR (neat)**:** ν = 2928, 2232, 1645, 1601, 1396, 727 cm^{-1}.

HRMS (EI): calculated for $C_7H_{11}ON^+$ = [M^+]: *m*/*z* = 125.0835, found: *m*/*z* = 125.0821.

3.3.5 Products of the Catalytic Conjugate Addition

4-Cyano-*N*,*N*-dimethylbutanamide (<u>206</u>)



206 was prepared according to *general procedure V* using *N*,*N*-dimethylacrylamide (39.6 mg, 0.40 mmol, 1.00 equiv) and acetonitrile (400 μL), in the presence of hexaphenylcarbodiphosphorane (2.20 mg, 4.00 μmol, 1.00 mol%) as the catalyst, at 40 °C for 3 h. **206** was purified by filtering through a pad of silica eluting EtOAc/PE (1:5; 5 mL).

Colourless liquid.

Yield: 48.5 mg (87%).

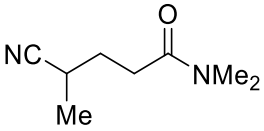
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.01 (s, 3H), 2.95 (s, 3H), 2.51 (t, *J* = 6.9 Hz, 2H), 2.48 (t, *J* = 6.9 Hz, 2H), 2.00 (pent, *J* = 6.9 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.7, 119.6, 37.0, 35.4, 30.9, 20.7, 16.6 ppm.

IR (neat): ν = 2938, 2245, 1637, 1497, 1456, 1430, 1398, 1253, 1142, 1081 cm^{-1}.

HRMS (EI): calculated for $C_7H_{12}N_2O^+$ = [M^+]: *m*/*z* = 140.0944; found: *m*/*z* = 140.0942.

4-Cyano-*N*,*N*,4-trimethylbutanamide (<u>303</u>)



303 was prepared according to *general procedure V* using *N*,*N*-dimethylacrylamide (39.6 mg, 0.40 mmol, 1.00 equiv) and propionitrile (400 μL), in the presence of hexaphenylcarbodiphosphorane (2.20 mg, 4.00 μmol, 1.00 mol%) as the catalyst, at 40 °C for 3 h. **303** was purified by filtering through a pad of silica eluting EtOAc/PE (1:5; 5 mL).

Colourless liquid.

Yield: 56.7 mg (92%).

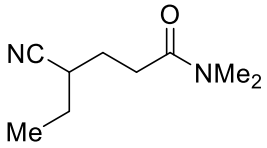
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.04 (s, 3H), 2.97 (s, 3H), 2.86 (ddd, *J* = 10.2, 7.1, 4.9 Hz, 1H), 2.56–2.53 (m, 2H), 2.04 (dtd, *J* = 13.8, 7.8, 4.9 Hz, 1H), 1.83 (dddd, *J* = 13.8, 10.2, 6.7, 6.0 Hz, 1H), 1.37 (d , *J* = 7.1 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.0, 122.8, 37.1, 35.5, 30.2, 29.4, 25.1, 18.2 ppm.

IR (neat): ν = 3377, 2938, 2237, 1640, 1504, 1221, 735 cm^{-1}.

HRMS (EI): calculated for $C_8H_{14}N_2O^+$ = [M^+]: *m*/*z* = 154.1100, found: *m*/*z* = 154.1097.

4-Cyano-*N*,*N*-dimethylhexanamide (<u>305</u>)



305 was prepared according to *general procedure V* using *N*,*N*-dimethylacrylamide (39.6 mg, 0.40 mmol, 1.00 equiv) and propionitrile (400 μL), in the presence of hexaphenylcarbodiphosphorane (2.20 mg, 4.00 μmol, 1.00 mol%) as the catalyst, at 40 °C for 3 h. **305** was purified by filtering through a pad of silica eluting EtOAc/PE (1:5; 5 mL).

Colourless liquid.

Yield: 20.1 mg (60%).

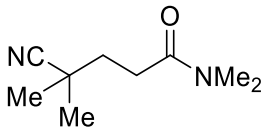
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.05 (s, 3H), 2.98 (s, 3H), 2.72 (dddd, *J* = 10.6, 8.3, 5.9, 4.7 Hz, 1H), 2.60–2.49 (m, 2H), 2.06 (dtd, *J* = 13.8, 7.8, 4.7 Hz, 1H), 1.83 (dddd, *J* = 13.8, 10.6, 6.9 Hz, 1H), 1.75–1.66 (m, 2H), 1.12 (t, *J* = 7.4 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 122.1, 37.1, 35.5, 32.8, 30.3, 27.3, 25.8, 11.6 ppm.

IR (neat): ν = 3705, 2938, 2236, 1636, 1400, 1057, 1011 cm^{-1}.

MS (EI): calculated for $C_9H_{16}N_2O^+$ = [M^+]: *m*/*z* = 168.1, found: *m*/*z* = 168.1.

4-Cyano-N,N,4,4-tetramethylbutanamide (<u>304</u>)



304 was prepared according to *general procedure V* using *N*,*N*-dimethylacrylamide (39.6 mg, 0.40 mmol, 1.00 equiv) and isopropionitrile (400 μL), in the presence of hexaphenylcarbodiphosphorane (2.20 mg, 4.00 μmol, 1.00 mol%) as the catalyst, at 40 °C for 24 h. **304** was purified by filtering through a pad of silica eluting EtOAc/PE (1:5; 5 mL)

Colourless liquid.

Yield: 67.3 mg (73%).

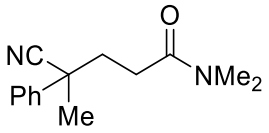
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.06 (s, 3H), 2.97 (s, 3H), 2.59–2.48 (m, 2H), 1.98–1.88 (m, 2H), 1.39 (s, 6H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.3, 124.7, 37.2, 36.0, 35.6, 32.0, 29.4, 26.7 ppm.

IR (neat): ν = 3493, 2930, 2234, 1639, 1398, 1144, 731 cm^{-1}.

MS (EI): calculated for $C_9H_{16}ON_2^+$ = [M^+]: *m*/*z* = 168.1259, found: *m*/*z* = 168.1264.

4-cyano-N,N,4-trimethyl-4-phenylbutanamide (306)



306 was prepared according to *general procedure V* using *N*, *N*-dimethylacrylamide (9.90 mg, 0.10 mmol, 1.00 equiv) and α-methylbenzylcyanide (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 20 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless liquid.

Yield: 21.5 mg (93%).

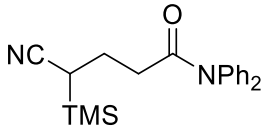
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.46 (m, 2H), 7.44–7.39 (m, 2H), 7.37–7.32 (m, 1H), 2.92 (s, 6H), 2.57–2.49 (m, 1H), 2.42–2.30 (m, 2H), 2.15 (ddd, *J* = 15.7, 10.5, 5.6 Hz, 1H), `1.77 (s, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 139.4, 129.1 (2C), 127.9, 125.4 (2C), 123.1, 42.1, 37.0, 36.8, 35.4, 29.5, 28.5 ppm.

IR (neat): ν = 2936, 2236, 1639, 1398, 1142, 910, 727, 698 cm^{-1}.

HRMS (EI): calculated for $C_{14}H_{18}ON_2^+$ = [M^+]: *m*/*z* = 230.1414, found: *m*/*z* = 230.1411.

4-cyano-N,N-diphenyl-4-(trimethylsilyl)butanamide (308)



308 was prepared according to *general procedure V* using acrylamide **330** (11.4 mg, 0.05 mmol, 1.00 equiv) and trimethylsilylacetonitrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 12 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless liquid.

Yield: 15.1 mg (90%).

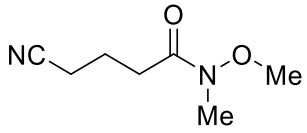
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–6.87 (m, 10H), 2.52 (t, *J* = 7.0 Hz, 1H), 2.45 (t, *J* = 6.8 Hz, 2H), 2.02 (pent, *J* = 6.8 Hz, 1H), 1.17–1.15 (m, 1H), 0.25 (s, 9H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 142.3, 130.0 (2C), 129.3 (4C), 126.3 (4C), 121.4 (2C), 119.4, 33.2, 21.0, 16.5, -0.6 (3C) ppm.

IR (neat): ν = 3680, 2957, 2208, 1670, 1254, 843, 692 cm^{-1}.

HRMS (EI): calculated for $C_{20}H_{24}ON_2Si^+$ = [M^+]: *m*/*z* = 336.1652, found: *m*/*z* = 336.1643.

4-cyano-N-methoxy-N-methylbutanamide (281)



281 was prepared according to *general procedure V* using acrylamide **331** (23.7 mg, 0.10 mmol, 1.00 equiv) and acetonitrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 20 h. **281** was purified by filtering through a pad of silica eluting EtOAc/PE (1:5; 5 mL).

Colourless solid.

Yield: 28.2 mg (91%).

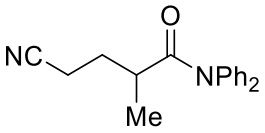
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.74 (s, 3H), 3.21 (s, 3H), 2.64 (t, *J* = 6.7 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 2.01 (tt, *J* = 6.7, 7.2 Hz, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5, 119.4, 61.3, 32.2, 29.9, 20.2, 16.7 ppm.

IR (neat): ν = 2924, 2245, 1653, 1420, 1179, 991 cm^{-1}.

HRMS (EI): calculated for $C_7H_{12}O_2N_2^+$ = [M^+]: *m*/*z* = 156.0893, found: *m*/*z* = 156.0888.

4-cyano-2-methyl-N,N-diphenylbutanamide (282)



282 was prepared according to *general procedure V* using acrylamide **332** (23.7 mg, 0.10 mmol, 1.00 equiv) and acetonitrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 20 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid.

Yield: 25.5 mg (92%).

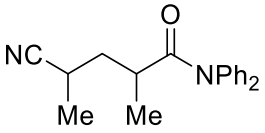
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.12 (m, 10H), 3.86 (dqd, *J* = 9.3, 6.9, 4.9 Hz, 1H), 2.51–2.39 (m, 2H), 2.16 (dddd, *J* = 13.6, 9.4, 6.7, 5.9 Hz, 1H), 1.70 (dddd, *J* = 13.6, 8.6, 7.0, 4.9 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.0, 130.0 (2C), 129.0 (2C), 128.8 (4C), 126.4 (4C), 119.5, 36.2, 29.4, 18.1, 15.2 ppm.

IR (neat): ν = 3061, 2916, 2247, 1663, 1491, 1267, 1003, 908, 729, 692 cm^{-1}.

HRMS (EI): calculated for $C_{18}H_{18}ON_2^+$ = [M^+]: *m*/*z* = 278.1414, found: *m*/*z* = 278.1429.

4-cyano-2,4-dimethyl-*N*,*N*-diphenylbutanamide (309)



309 was prepared according to *general procedure V* using acrylamide **332** (23.7 mg, 0.10 mmol, 1.00 equiv) and propionitrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 15 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid.

dr =1:1.5

Yield: 25.6 mg (88%).

Mp. = 62–63 °C

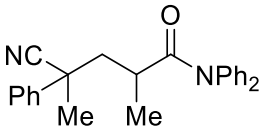
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.13 (m, 10H), 2.96 (ddq, *J* = 13.7, 6.8, 3.4 Hz, 1H, major), 2.86–2.74 (m, 1H), 2.65 (dqd, *J* = 9.3, 7.1, 5.9 Hz, 1H, minor), 2.19 (ddd, *J* = 13.7, 9.3, 6.8 Hz, 1H, minor), 2.13 (ddd, *J* = 13.4, 11.0, 4.5 Hz, 1H, major), 1.64 (ddd, *J* = 13.9, 7.0, 5.9 Hz, 1H, minor), 1.52 (ddd, *J* = 13.4, 11.3, 3.7 Hz, 1H, major), 1.32 (d, *J* = 7.0 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H, minor), 1.17 (d, *J* = 6.9 Hz, 3H, major) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.4 (minor), 175.2 (major), 130.0 (2C), 129.0 (4C), 128.3 (2C), 126.5 (4C), 123.0 (major), 122.3 (minor), 38.7 (major), 38.0 (minor), 36.0 (major), 35.5 (minor), 29.7, 24.0 (major), 23.5 (minor), 18.8 (major), 18.6 (minor), 18.3 (major), 17.9 (minor) ppm.

IR (neat): ν = 2974, 2916, 2361, 2237, 1665, 1491, 1385, 1271, 756, 692 cm^{-1}.

HRMS (EI): calculated for $C_{19}H_{20}ON_2^+ = [M^+]$: *m*/*z* = 292.1570, found: *m*/*z* = 292.1578.

4-cyano-2,4-dimethyl-*N*,*N*,4-triphenylbutanamide (310)



310 was prepared according to *general procedure V* using acrylamide **332** (23.7 mg, 0.10 mmol, 1.00 equiv) and α-methylbenzylcyanide (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 15 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid.

Yield: 28.0 mg (76%).

dr = 1:1.6

Mp: 90–91 °C

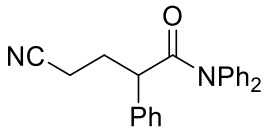
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.41 (m, 2H), 7.41–7.33 (m, 4H), 7.32–7.25 (m, 4H), 7.25–7.12 (br m, 2H), 7.11–7.00 (br m, 1H), 7.00–6.86 (br m, 1H), 2.97 (dd, *J* = 14.7, 6.9 Hz, 1H), 2.90 (dd, *J* = 14.3, 8.7 Hz, 1H, minor), 2.72–2.65 (m, 1H, minor), 2.63 (td, *J* = 6.9, 3.9 Hz, 1H), 1.91 (dd, *J* = 14.7, 3.9 Hz, 1H), 1.83 (dd, *J* = 14.3, 2.7 Hz, 2H, minor), 1.74 (s, 3H, minor), 1.66 (s, 3H), 1.28 (d, *J* = 7.00 Hz, 3H), 1.10 (d, *J* = 6.9 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.4, 142.3, 140.3, 139.5, 129.7, 129.0, 128.8, 128.6, 127.9, 127.7, 126.7, 126.5, 126.2, 126.0, 125.3, 123.2, 123.0, 45.6 (minor), 44.8, 42.0, 41.9 (minor) 34.9, 34.8 (minor), 29.7 (minor), 29.5, 28.4 ppm.

IR (neat): ν = 3061, 2976, 2236, 1667, 1491, 1273, 758, 698 cm^{-1}.

HRMS (EI): calculated for $C_{25}H_{24}ON_2^+ = [M^+]$: *m*/*z* = 368.1883, found: *m*/*z* = 368.1902.

4-cyano-N,N,2-triphenylbutanamide (283)



283 was prepared according to *general procedure V* using acrylamide **289** (15.0 mg, 0.10 mmol, 1.00 equiv) and acetonitrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 20 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless tar.

Yield: 13.4 mg (40%).

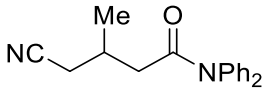
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5H), 7.26–7.22 (m, 3H), 7.22–7.13 (m, 3H), 7.05–6.96 (m, 4H), 3.93–3.87 (m, 1H), 2.52–2.38 (m, 2H), 2.30–2.21 (m, 1H), 2.06–1.96 (m, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 138.0, 129.6 (2C), 129.3 (2C), 128.9 (2C), 128.8 (4C), 127.9 (4C), 127.6 (2C), 126.3, 119.3, 48.7, 30.2, 15.3 ppm.

IR (neat): ν = 3061, 2918, 2359, 1666.5, 1491, 1279, 756.1, 700 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{20}ON_2^+ = [M^+]$: *m*/*z* = 340.1570, found: *m*/*z* = 340.1572.

4-cyano-3-methyl-*N*,*N*-diphenylbutanamide (284)



284 was prepared according to *general procedure V* using acrylamide **337** (11.9 mg, 0.05 mmol, 1.00 equiv) and acetonitrile (100 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 10.0 mol%) as the catalyst, at 80 °C for 42 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless oil.

Yield: 19.5 mg (70%).

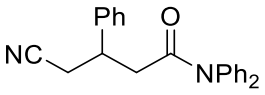
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73–7.09 (m, 10H), 2.86 (dqd, *J* = 9.4, 6.8, 4.8 Hz, 1H), 2.52–2.39 (m, 2H), 2.17 (dddd, *J* = 13.7, 9.4, 6.7, 5.9 Hz, 1H), 1.70 (dddd, *J* = 13.5, 8.5, 7.0, 4.8 Hz, 1H), 1.19 (d, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 142.8 (2C), 142.4 (4C), 129.2 (2C), 123.8 (4C), 118.4, 40.3, 27.6, 23.8, 22.7 ppm.

IR (neat): ν = 2918, 2849, 2361, 1668, 1491, 1346, 1250, 735, 700 cm^{-1}.

HRMS (EI): calculated for $C_{18}H_{18}N_2O^+$ = [M^+]: *m*/*z* = 278.1414, found: *m*/*z* = 278.1412.

4-cyano-*N*,*N*-3-triphenylbutanamide (285)



285 was prepared according to *general procedure V* using acrylamide **336** (29.9 mg, 0.10 mmol, 1.00 equiv) and acetonitrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 20 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid.

Yield: 30.2 mg (89%).

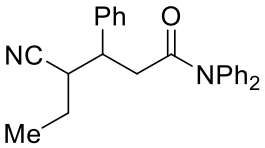
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.28 (m, 8H), 7.26–7.17 (m, 3H), 7.17–7.08 (m, 4H), 3.72–3.64 (m, 1H), 2.91–2.67 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.2, 142.3, 141.0 (2C), 130.0, 129.9 (4C), 128.6, 127.7 (2C), 127.3 (4C), 126.4, 118.3 (2C), 39.7, 38.6, 29.7, 24.0 ppm.

IR (neat): ν = 2916, 2849, 2253, 1662, 1492, 1383, 700 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{20}ON_2^+$ = [M^+]: *m*/*z* = 340.1570, found: *m*/*z* = 340.1569.

4-Ethyl-4-cyano-3-phenyl-*N*,*N*-diphenyl-pentanamide (307)



307 was prepared according to *general procedure V* using acrylamide **336** (29.9 mg, 0.10 mmol, 1.00 equiv), *n*-butyronitrile (100 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) and stirred at 40 °C for 16 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid

Yield: 30.9 mg (84%).

dr = 1:1.5

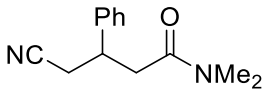
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.22 (m, 10 H), 7.22–7.08 (m, 4H), 7.06–6.87 (br m, 1H), 3.58–3.48 (m, 1H), 3.18–3.11 (m, 1H, minor), 2.96–2.89 (m, 1H), 2.83–2.78 (m, 1H, minor), 2.78–2.71 (m, 1H),1.58–1.45 (m, 1H), 1.43–1.31 (m, 1H, minor), 1.08–1.00 (m, 3H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.6, 170.3(minor), 142.5, 140.1, 139.2, 130.0, 128.8, 128.6, 128.5, 128.1, 127.7, 127.6, 126.4, 121.0 (minor), 120.9, 44.2 (minor), 43.0, 39.5 (minor), 39.4, 39.1 (minor), 38.2, 24.3, 23.9 (minor), 12.0, 11.5 (minor) ppm.

IR (neat)**:** ν = 3705, 2980, 1381, 1055, 903, 725 cm^{-1}.

HRMS (EI): calculated for $C_{25}H_{24}O_3N_2^+$ = [M^+]: *m*/*z* = 368.1883, found: *m*/*z* = 368.1870.

4-cyano-*N*,*N*-dimethyl-3-phenylbutanamide (<u>286</u>)



286 was prepared according to *general procedure V* using acrylamide **335** (23.7 mg, 0.10 mmol, 1.00 equiv) and acetonitrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 20 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless oil.

Yield: 18.1 mg (84%).

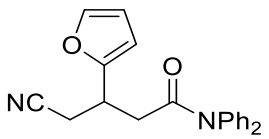
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.40–7.36 (m, 2H), 7.34–7.29 (m, 3H), 3.63 (ddt, *J* = 9.3, 7.0, 4.8 Hz, 1H), 3.00 (s, 3H), 2.96 (s, 3H), 2.95–2.69 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ 170.0, 141.6, 128.9 (2C), 127.6, 127.1 (2C), 118.5, 37.7, 37.5, 37.1, 35.5, 24.0 ppm.

IR (neat): ν = 2930, 2243, 1634, 1398, 1145, 761, 700 cm^{-1}.

HRMS (EI): calculated for $C_{13}H_{16}ON_2^+$ = [M^+]: *m*/*z* = 216.1257, found: *m*/*z* = 216.1260.

4-cyano-3-(furan-2-yl)-*N*,*N*-diphenylbutanamide (<u>288</u>)



288 was prepared according to *general procedure V* using acrylamide **341** (14.5 mg, 0.05 mmol, 1.00 equiv) and acetonitrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 80 °C for 39 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid.

Yield: 15.8 mg (96%).

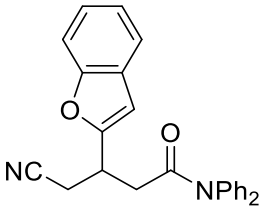
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49–7.34 (m, 5H), 7.33 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.31 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.14 (dt, *J* = 3.3, 0.8 Hz, 1H) 3.77 (tt, *J* = 6.9, 6.1 Hz, 1H), 2.95–2.65 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 153.7, 142.3, 142.0, 130.1 (2C), 129.0 (2C), 128.6 (2C), 126.4 (2C), 117.8, 110.4, 106.4, 37.6, 32.4, 21.7 ppm.

IR (neat): ν = 2916, 2849, 2247, 1667, 1593, 1491, 1377, 1290, 756, 702 cm^{-1}.

HRMS (EI): calculated for $C_{21}H_{18}O_2N_2^+$ = [M^+]: *m*/*z* = 330.1363, found: *m*/*z* = 330.1374.

3-(1-benzofuran-2-yl)-4-cyano-*N*,*N*-diphenylbutanamide (289)



289 was prepared according to *general procedure V* using acrylamide **362** (23.7 mg, 0.10 mmol, 1.00 equiv) and acetonitrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 20 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid.

Yield: 48.5 mg (87%).

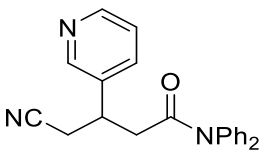
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.56–7.50 (m, 1H), 7.39–7.35 (m, 5H), 7.34–7.29 (m, 4H), 7.26–7.18 (m, 5H), 6.67 (s, 1H), 3.97–3.90 (m, 1H), 3.01 (dd, *J* = 55.7, 5.6Hz, 1H), 2.92 (ddd, *J* = 72.4, 21.7, 5.5 Hz, 1H), 2.86 (dd, *J* = 8.6, 5.5 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 156.5, 154.9, 129.7, 128.5, 126.3, 126.1, 124.3 (4C), 122.9, 121.0 (4C), 120.3, 117.6, 111.3, 111.0, 110.6, 103.6, 37.4, 32.9, 21.4 ppm.

IR (neat): ν = 3061, 2916, 2849, 2247, 1663, 1491, 1273, 752 cm^{-1}.

HRMS (EI): calculated for $C_{25}H_{20}O_2N_2^+$ = [M^+]: *m*/*z* = 380.1519, found: *m*/*z* = 380.1510.

4-cyano-*N*,*N*-diphenyl-3-(pyridin-3-yl)butanamide (287)



287 was prepared according to *general procedure V* using acrylamide **342** (30.0 mg, 0.10 mmol, 1.00 equiv) and acteonitrile (200 μL), in the presence of hexaphenylcarbo-

diphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 15 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Pale yellow liquid.

Yield: 29.0 mg (85%).

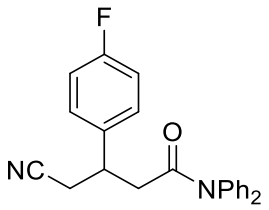
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.49 (d, *J* = 2.1 Hz, 1H), 7.61–7.57 (m, 1H), 7.50–7.29 (m, 6H), 7.26–7.10 (m, 5H), 3.72 (pent, *J* = 6.6 Hz, 1H), 2.89 (dd, *J* = 30.0, 7.0 Hz, 1H), 2.86 (dd, *J* = 29.4, 7.0 Hz, 1H), 2.77 (dd, *J* = 36.3, 6.6 Hz,1H), 2.74 (dd, *J* = 36.3, 6.6 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 149.2 (4C), 148.9 (4C), 142.1, 135.0 (2C), 130.2, 129.1, 128.6, 126.3, 123.7 (2C), 117.7, 39.1, 36.2, 23.8 ppm.

IR (neat): ν = 3067, 2918, 2851, 1668, 1491, 1383, 704 cm^{-1}.

HRMS (EI): calculated for $C_{22}H_{20}ON_3^+$ = [M^+]: *m*/*z* = 342.1601, found: *m*/*z* = 342.1602.

4-cyano-3-(4-fluorophenyl)-*N*,*N*-diphenylbutanamide (<u>291</u>)



291 was prepared according to *general procedure V* using acrylamide **350** (15.9 mg, 0.05 mmol, 1.00 equiv) and acetonitrile (100 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 10.0 mol%) as the catalyst, at 40 °C for 70 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid.

Yield: 16.1 mg (90%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47–7.30 (br m, 5H), 7.18–7.06 (br m, 7H), 7.02 (ap t, *J* = 8.6 Hz, 2H), 3.66 (ap pent, *J* = 6.9 Hz, 1H), 2.80 (d, *J* = 22.5, 7.1 Hz, 1H), 2.77 (dd, *J* = 22.5, 7.1 Hz, 1H), 2.70 (dd, *J* = 28.1, 6.0 Hz, 1H), 2.67 (dd, *J* = 27.3, 6.0 Hz, 1H) ppm.

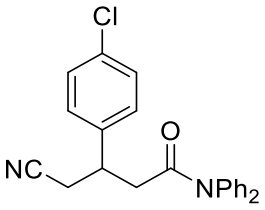
^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.0, 161.8 (d, *J* = 246.5 Hz), 142.2, 136.7, 130.1 (2C), 129.1 (4C), 128.9 (d, *J* = 8.0 Hz, 2C), 128.5 (4C), 128.5 (2C), 118.1, 115.9 (d, *J* = 21.4 Hz, 2C), 39.8, 37.9, 24.2 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ = -110.0 ppm.

IR (neat): ν = 3696, 2918, 1665, 1491, 1055, 1032, 1012, 702 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{19}FN_2O^+$ = [M^+]: *m*/*z* = 358.1476, found: *m*/*z* = 358.1493.

4-cyano-3-(4-chlorophenyl)-*N*,*N*-diphenylbutanamide (<u>292</u>)



292 was prepared according to *general procedure V* using acrylamide **360** (16.7 mg, 0.05 mmol, 1.00 equiv) and acetonitrile (100 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 10.0 mol%) as the catalyst, at 40 °C for 70 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid.

Yield: 17.0 mg (91%).

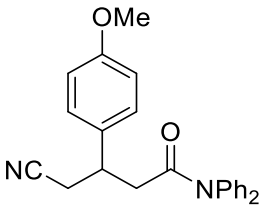
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.34 (br m, 5H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.23–7.06 (br m, 5H), 7.13 (d, *J* = 8.4 Hz, 2H), 3.68–3.61 (m, 1H), 2.80 (d, *J* = 26.2, 7.5 Hz, 1H), 2.77 (dd, *J* = 25.1, 1.7 Hz, 1H), 2.70 (dd, *J* = 30.3, 7.0 Hz, 1H), 2.67 (dd, *J* = 28.8, 6.9 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 142.2 (2C), 139.4 (2C), 133.6 (2C), 130.1, 129.1 (4C), 128.7 (4C), 128.3, 126.2 (2C), 118.0, 39.6, 37.9, 24.0 ppm.

IR (neat): ν = 2916, 2848, 2247, 1667, 1491, 1379, 908, 702 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{19}ClN_2O^+$ = [M^+]: *m*/*z* = 374.1180, found: *m*/*z* = 374.1188.

4-cyano-3-(4-methoxyphenyl)-*N*,*N*-diphenylbutanamide (<u>294</u>)



294 was prepared according to *general procedure V* using acrylamide **352** (23.7 mg, 0.10 mmol, 1.00 equiv) and acetonitrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 90 °C for 22 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid.

Yield: 31.5 mg (85%).

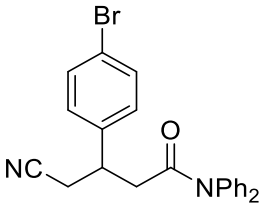
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51–7.28 (m, 5H), 7.24–7.04 (m, 7H), 6.89–6.83 (m, 2H), 3.80 (s, 3H), 3.61 (pent, *J* = 7.3 Hz, 1H), 2.79 (dd, *J* = 22.2, 7.3 Hz, 1H), 2.73 (ddd, *J* = 34.2, 22.2, 7.0 Hz, 2H), 2.66 (dd, *J* = 25.5, 6.4 Hz, 1H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.3, 159.0 (2C), 142.3 (2C), 133.0 (2C), 130.0, 129.0, 128.6 (4C), 128.3, 126.4, 188.4, 114.2 (4C), 55.3, 39.9, 37.8, 24.2 ppm.

IR (neat): ν = 2916.4, 2849, 1667, 1514, 1250, 702 cm^{-1}.

HRMS (EI): calculated for $C_{24}H_{22}O_2N_2^+$ = [M^+]: *m*/*z* = 370.1676, found: *m*/*z* = 370.1693.

4-cyano-3-(4-bromophenyl)-*N*,*N*-diphenylbutanamide (293)



293 was prepared according to *general procedure V* using acrylamide **351** (23.7 mg, 0.10 mmol, 1.00 equiv) and acetontrile (200 μL), in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) as the catalyst, at 40 °C for 20 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless solid.

Yield: 32.8 mg (79%).

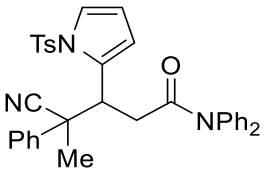
^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.4 Hz, 2H), 7.44–7.28 (br m, 5H), 7.22–7.09 (br m, 5H), 7.07 (d, *J* = 8.4 Hz, 2H), 3.63 (ap pent, *J* = 6.8 Hz, 1H), 2.83–2.63 (m, 4H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 142.2, 140.0, 132.0 (2C), 130.1 (4C), 129.0 (2C), 128.5 (4C), 126.3 (2C), 121.6 (2C), 117.9, 39.6, 38.0, 23.9 ppm.

IR (neat): ν = 2916, 2849, 2251, 1663, 1489, 1379, 907, 727 cm^{-1}.

HRMS (EI): calculated for $C_{23}H_{19}ON_2Br^+$ = [M^+]: *m*/*z* = 418.0675, found: *m*/*z* = 418.0654.

4-cyano-4-methyl-3-[1-(4-toluenesulfonyl)pyrrol-2-yl]-*N*,*N*,4-triphenylbutanamide (311)



311 was prepared according to general procedure V using acrylamide **344** (22.1 mg, 0.1 mmol, 1.00 equiv), α-methylbenzylcyanide (100 μL) in the presence of hexaphenylcarbodiphosphorane (2.70 mg, 5.00 μmol, 5.00 mol%) and stirred at 40 °C for 16 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Tan solid

Yield: 25.4 mg (44%).

dr = 1:5

Major ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.04–7.98 (m, 2H), 7.70 (ddd, *J* = 7.8, 3.9, 1.2 Hz, 2H), 7.51–7.46 (m, 2H), 7.42–7.38 (m, 2H), 7.33–7.31 (m, 1H), 7.23–7.19 (m, 3H), 7.14–7.08 (m, 2H), 7.02–6.82 (m, 3H), 6.80–6.56 (m, 3H), 6.37–6.28 (m, 2H), 5.07 (dt, *J* = 9.8, 1.4 Hz, 1H), 2.73 (ddd, *J* = 15.6, 9.8, 4.4 Hz, 1H), 2.40 (t, *J* = 4.3 Hz, 1H), 2.37 (s, 3H), 1.60 (s, 3H) ppm.

Minor ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.50–7.32 (m, 4H), 7.25 (dd, *J* = 8.6, 0.6 Hz, 3H), 7.19 (tt, *J* = 7.3, 1.2 Hz, 3H), 7.14–7.09 (m, 3H), 7.08–7.07 (m, 2H), 7.05–7.01 (m, 2H), 6.08 (t, *J* = 3.4 Hz, 1H), 5.94–5.91 (m, 1H), 2.91 (dd, *J* = 16.4, 6.0 Hz, 1H), 2.62 (dd, *J* = 16.4, 6.9 Hz, 1H), 1.83 (s, 3H), 1.56 (s, 3H) ppm.

Major ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.6, 144.7, 142.2, 139.7, 136.3, 134.3 (2C), 129.8 (4C), 129.2 (2C), 128.4 (2C), 128.1 (2C), 127.8 (2C), 126.2 (4C), 123.6 (2C), 121.5, 113.5 (2C), 112.3 (2C), 50.8, 41.2, 37.9, 27.1, 21.7 ppm.

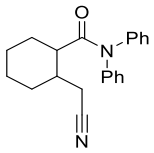
Minor ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.1, 144.7, 138.1, 136.4, 133.7 (2C), 130.0, 129.8 (4C), 128.7, 128.0 (2C), 127.7 (2C), 127.6 (2C), 126.5 (4C), 126.1, 123.1, 122.9, 114.1 (2C), 111.4 (2C), 47.7, 41.4, 39.1, 29.7, 26.0, 21.7 ppm

Major IR (neat)**:** ν = 3061, 1665, 1491, 1366, 1175, 910, 700, 673 cm^{-1}.

Major HRMS (EI): calculated for $C_{35}H_{31}O_3N_3S^+$ = [M^+]: *m*/*z* = 573.2080, found: *m*/*z* = 573.2057.

Major HRMS (EI): calculated for $C_{35}H_{31}O_3N_3S^+$ = [M^+]: *m*/*z* = 573.2080, found: *m*/*z* = 573.2084.

2-(cyanomethyl)-*N*,*N*-diphenylcyclohexane-1- carboxamide (313)



313 was prepared according to general procedure V using acrylamide **369** (13.9 mg, 0.05 mmol, 1.00 equiv), MeCN (100 µL), and CDP (10 mol%) and stirred at 40 °C for 16 h. The crude reaction mixture was purified by PTLC eluting EtOAc/hexane (20:80).

Colourless liquid

Yield: 13.6 mg (86%).

dr = 1:1

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.35 (m, 4H), 7.34–7.14 (m, 6H), 4.22–4.18 (m, 1H), 3.14 (dt, *J* = 8.4, 4.1 Hz, 1H), 2.26–2.17 (m, 1H), 2.14–2.05 (m, 1H), 1.89 (ddt, *J* = 13.3, 6.6, 3.1 Hz, 1H) 1.83–1.74 (m, 1H), 1.68–1.60 (m, 1H), 1.59–1.51 (m, 2H), 1.44–1.36 (m, 1H), 0.94–0.84 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.3, 143.1 (2C), 129.5 (2C), 129.0 (4C), 127.2 (4C), 59.4, 44.8, 33.5, 31.9, 24.6, 22.9, 21.7, 14.1 ppm.

IR (neat)**:** ν = 2924, 2853, 2361, 1676, 1491, 1267, 702 cm^{-1}.

MS (EI): calculated for $C_{21}H_{22}N_2O^+$ = [M^+]: *m*/*z* = 318.1, found: *m*/*z* = 318.1.

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